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Topical Review

Marijuana Poisoning

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Key Points

1. A range in %THC is possible depending on the formulation and parts of the plant used
2. Marijuana ingestion rarely leads to fatality

Summary

- Dogs and cats are very susceptible to marijuana toxicosis but dogs are much more often affected
- Marijuana poisoning in dogs results from
    - Inhalation of secondhand smoke
    - Ingestion of the seeds, stems, leaves, and flowers
    - Ingestion of products made from marijuana leaves (cookies, suckers, brownies, teas, etc.)
    - Ingestion of products made with concentrated tetrahydrocannabinol (THC) or hashish oil
- ‘‘Marijuana’’ refers to any part of the plant, but generally, it has come to refer to the dried tobacco-like preparations of the leaves and flowers
- Cannabis sativa plants produce more than 60 chemical substances called cannabinoids
    - The major psychoactive constituent in the plant is the cannabinoid THC
    - The only other cannabinoids in marijuana shown to produce psychoactive effects are cannabinol and cannabidiol
        - Less than 10 times the potency of THC
    - The THC content in marijuana can range from 0.4% to almost 20% depending upon the cultivation techniques (amount of light, moisture, soil type, soil pH, nutrients, elements, and fertilizers provided)
    - Hashish is made from the resin collected from the tops of flowering plants and often has THC levels that exceed 10%
    - Hash oil contains much more concentrated THC with values often reaching 20% or even higher
- By 2010 synthetic cannabinoids appeared
    - Marketed as an herbal incense
    - Potent
    - Names include JWH-11, ‘‘Spice,’’ ‘‘K2,’’ ‘‘Skunk,’’ ‘‘Wild Greens,’’ ‘‘Head Trip,’’ ‘‘Purple Haze,’’ and ‘‘Zombie Matter
    - Smoking these incenses produced paranoia, hallucinations, tremors, seizures, injury, and death

    - Banned with the passage of the Synthetic Drug Control Act in 2011
- Peak brain levels of THC may not be achieved for a few hours, but may last longer when ingested than through inhalation
- Butter containing THC may result in higher %THC than that found in the plant
    - Two reported deaths following THC-butter ingestion
- THC has a wide safety margin in dogs
    - Minimum lethal oral dose greater than 3 g/kg
    - This dose is 1000 times the dosage where behavioral effects are observed
    - A true toxic dose for THC in mg/kg is difficult to determine because the degree of purity for marijuana varies so greatly and exposure also depends upon the route of exposure
- Oral absorption of THC can be increased with the ingestion of fatty foods
    - The onset of effects usually begins within 60 minutes
- THC is highly lipid soluble and is distributed into fat, liver, brain, and kidney
- The majority of THC is metabolized by the liver, with the THC converted to the primary metabolite, 11- hydroxy-D-9-THC
- THC and its metabolites are excreted in the urine (15%) and feces
- Enterohepatic recirculation is a prominent feature of marijuana metabolism
- Adipose storage produces a biological half-life for THC of approximately 30 hours
- 80% of THC is excreted from the body in about 5 days (approximately 5 half-lives, dogs)
- Two specific cannabinoid receptors have been identified
    - CB1: receptors are distributed throughout the brain, particularly in the basal ganglia, substantia nigra, globus pallidus, hippocampus, cerebellum, and frontal regions of the cerebral cortex
    - Found on the presynaptic side of CNS synapses and inhibit acetylcholine, L-glutamate, gamma-aminobutyric acid, noradrenaline, dopamine, and serotonin
    - CB2: receptors are found peripherally and are not detected in the central nervous system
        - Responsible for the analgesic effect?
        - May play a role in mediating release of cytokines
- In addition to neurologic effects, ingestion of large amounts of plant material may irritate the gastrointestinal tract and cause vomiting
- The various effects of THC exposure (including time of onset, duration of effect, and severity of clinical signs), depend upon the dose and the route of administration of the drug
- Clinical signs include ataxia and incoordination, hypersalivation, depression, disorientation, hypothermia, mydriasis, bradycardia, vomiting, and tremors
- +/- stupor, nystagmus, apprehension, vocalization, hyperexcitability, tachypnea, tachycardia, hyperthermia, and hyperesthesia with heightened sensitivity to motion, light, and sound

- In a recent retrospective study, ataxia and depression were the most common clinical findings at presentation for dogs with THC poisoning
- Duration of clinical signs can range from 1-3 days, with 24 hours being the average time for signs to persist
- Diagnostics
    - The use of human urine drug- screening tests in dogs remains controversial
    - Gas chromatography-mass spectrometry is also used in humans to detect marijuana but it may take several days to perform and obtain results
    - Currently, there is no single scientific laboratory test (enzyme-linked immunosorbent assay, gas chromatography, liquid chromatography, or mass spectrometry) that reliably detects THC in the urine of dogs
- Treatment
    - There is no specific antidote for cannabis
    - Emesis may be unrewarding as THC has been shown to have a significant antiemetic effect
        - Emesis can be initiated if the ingestion was recent (within the last 2 hours) but should never be employed if signs of CNS stimulation are present, if the animal is severely agitated, or if the animal is severely depressed or unresponsive
    - Activated charcoal
    - Quiet, supportive, and protective environment
    - Severe CNS stimulation can be treated with a benzodiazepine
    - Chlorpromazine (0.5-1.0 mg/kg IV) is recommended to counter acute anxiety
    - IVF may be given to counter dehydration in animals that have vomited severely and also to counter hypothermia
    - Animals whose vomiting becomes persistent or severe may be treated with antiemetics
    - While hospitalized, temperature, pulse rate, and respiration should be monitored every 2 hours
    - ILE
    - No long-term histologic lesions have been described in animals poisoned by THC

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Selective Serotonin Reuptake Inhibitor Exposure

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Key Points

1. SSRI ingestion rarely leads to fatality
2. Treatment focuses on supportive care

Summary

- Many antidepressants inhibit serotonin or norepinephrine reuptake or both to achieve their clinical effect
- The SSRIs are as effective as tricyclic antidepressants in treatment of major depression with less significant side effects
    - Despite their widespread use and easy availability, there is surprisingly little information in previous reports to accurately define a minimum acute dosage of any SSRI
    - SSRIs as a class have a wide margin of safety
    - Doses greater than 5 times the single therapeutic dose warranted referral to an emergency room

Median Dose Necessary to Cause Symptomatic SSRI Toxicity in Dogs[2]

Drug	Symptomatic Median Dose Range (mg/kg)
(1) Citalopram	4.2 mg/kg (n = 10 dogs)
(2) Escitalopram	4.4 mg/kg (n = 7 dogs)
(3) Fluoxetine	15.9 mg/kg (n = 12 dogs)
(4) Fluvoxamine	1.5 mg/kg (n = 1 dog)
(5) Paroxetine	7.7 mg/kg (n = 5 dogs)
(6) Sertraline	11.6 mg/kg (n = 22 dogs)

- SSRIs act specifically on synaptic serotonin concentrations by blocking its reuptake in the presynapse and increasing levels in the presynapticmembrane
- Serotonin is a biogenic amine produced from the essential amino acid tryptophan
- The majority of the body's serotonin is synthesized within the CNS and enterochromaffin cells
- Serotonin within the CNS is stored in the presynaptic vesicles of the serotonergic neurons, pineal gland, and catecholaminergic neurons
- The presynaptic membrane releases serotonin and binds to serotonin-specific receptors on the postsynaptic membrane

- In addition, serotonin may bind to autoreceptors on the presynaptic membrane, which acts as a negative feedback to further serotonin release
- Serotonin is removed from the synaptic cleft by binding to a selective serotonin transporter
    - This molecule transports the serotonin into the presynaptic cytosol
    - The cytosolic serotonin is metabolized by monoamine oxidase (MAO) or repackaged in vesicles
- The effect of at the postsynaptic membrane is determined by the amount of serotonin available to bind 5-hydroxytryptamine (5-HT) receptors
- SSRIs act more specifically on synaptic serotonin concentrations with minimal effects on catecholamine, acetylcholine, and histamine as compared with other serotonin-modulating drugs
    - This specificity of SSRIs minimizes the adverse effects seen with MAOIs and tricyclic antidepressants
- All of the SSRIs are well- absorbed after oral ingestion, and are highly protein bound
- All SSRIs are metabolized in the liver and have numerous active metabolites
- The SSRIs have diverse elimination patterns, however most are excreted in the urine
    - Sertraline excreted in the bile in dogs
- Clinical signs of SSRI overdose result from excessive amounts of serotonin in the central nervous system
    - Dogs
        - Low doses: hypersalivation, anorexia, agitation, vomiting, and tremors are typically observed
        - 'Significant overdose': vomiting, diarrhea, weakness, ataxia, nystagmus, head tilt, bradycardia, aggressive behavior, tremors, and seizures
            - Signs are dose dependent and usually appear within 1 hour
            - The higher the dose ingested, the greater the chances for development of the serotonin syndrome
            - Potentially life-threatening complication of antidepressant drug therapy
            - Often goes unidentified due to its non- specific symptoms
            - Autonomic instability, altered mental status, seizures, agitation, myoclonus, hyperreflexia, shivering, tremors, vomiting, diarrhea, and hyperthermia, and extrapyramidal syndrome including muscle rigidity and hyperthermia
            - Produced most often by the concurrent use of 2 or more xenobiotics that increase serotonin activity in the CNS
            - No single clinical test is currently available to confirm SSRI toxicosis

- For all SSRIs, hyperthermia and gastrointestinal and neurologic signs are the most common clinical manifestations of overdose
- In some dogs, GI upset and CNS signs have been noted when fluoxetine was used at therapeutic doses for separation anxiety treatment

Table 5
Clincial Signs Reported In Dogs Following SSRI Overdose

- Anorexia
- Hypersalivation
- Agitation
- Vomiting
- Diarrhea
- Tremors
- Weakness
- Ataxia
- Nystagmus
- Head tilt
- Bradycardia
- Seizures
- Aggressive behavior
- Hyperthermia
- Mydriasis
- Rigidity

Table 4
Drugs with Potential to Cause Serotonin Syndrome

SSRIs	**Miscellaneous**
Citalo pram	Buspi rone
Fluoxetine	Carbamazepine
Fluvoxamine	Cocaine
Paroxetine	Cyclobenzaprine
	Dextromethorphan
SNRIs	Ergot Alkaloids
	Fentanyl
Duloxetine	5 Hydroxytryptophan
Sibutramine	Linezolid
Venlaxafine	Lithium
	L-Tryptophan
TRIPTANs	Meperidine
	Methamphetamine
Almotriptan	Methylene blue
Eletriptan	Metoclopramide
Frovatriptan	Mirtazapine
Naratriptan	Ondansetron
Rizatriptan	Phenelzine
Sumatriptan	Selegiline
Zolmitriptan	St. John's Wort
	Tramadol
	Tranyloypromine
	Trazodone
	Tricyclic antidepressants
	Valproic acid

- Most patients recover from serotonin syndrome after 24 hours of discontinuing the SSRI and initiating supportive care
- Goals of treatment in this intoxication are to support the animal, prevent further absorption of the drug, support the central nervous system, control hyperthermia, and halt any seizure activity
- The prognosis in animals that receive treatment is excellent
- No characteristic or classic histopathologic lesions result from SSRI toxicosis

Questions

1. Which of the following THC formulations are typically considered to have increased potency?
    a. Hemp
    b. Hashish
    c. Marijuana-infused butter
    d. Medical grade marijuana
    e. Synthetic cannbiniods
2. $T_{1/2}$ of THC is:
    a. 5 hours
    b. 15 hours
    c. 30 hours
    d. 3 days
    e. 5 days
3. Why do SSRIs less commonly result in toxicity as compared with other serotonin modulators?
4. T/F: SSRIs are metabolized in the liver, resulting in inactive metabolites.

Answers

1. Which of the following THC formulations are typically considered to have increased potency?
    a. Hemp
    b. Hashish
    c. Marijuana-infused butter
    d. Medical grade marijuana
    e. Synthetic cannbiniods
2. $T_{1/2}$ of THC is:
    a. 5 hours
    b. 15 hours
    c. 30 hours
    d. 3 days
    e. 5 days
3. Why do SSRIs less commonly result in toxicity as compared with other serotonin modulators?
    a. They have high synaptic cleft sensitivity
4. T/**F**: SSRIs are metabolized in the liver, resulting in inactive metabolites.