Gas and Grass: Anesthetic Considerations for Cannabis Users

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I. THE HISTORY OF CANNABIS LEGALITY IN THE UNITED STATES

A. The Controlled Substances Act of 1970 led to the classification of cannabis products as Schedule 1 substances (Alexander et al., 2019)

i. Per the Federal government, schedule 1 substances currently have no accepted medical use in the US, a lack of accepted safety for use under medical supervision, and a high potential for abuse (Drug Enforcement Agency, n.d.)

ii. Includes substances such as cannabis, LSD, heroin, and ecstasy (Drug Enforcement Agency, n.d.)

iii. While medical cannabis is currently being used to treat medical conditions such as AIDS wasting, epilepsy, neuropathic pain, spasticity, multiple sclerosis, and cancer, the Federal Drug Administration (FDA) has not approved cannabis for the treatment of any disease or condition.

iv. Though cannabis is considered unapproved, three cannabinoids or cannabis-derived drug products have been approved for the treatment of seizures related to Lennox-Gastaut or Drager syndrome, chemotherapy-induced nausea and vomiting, and anorexia with weight loss in AIDs patients (Federal Drug Administration, 2020).

B. In 1996, California became the first state to legalize medical marijuana (Pacula & Smart, 2019)

C. In 2012, Colorado and Washington became the first states to approve legalization of cannabis for recreational use (Pacula & Smart, 2019).

D. At the time of this podcast, 33 states including the District of Columbia have embraced medical marijuana legalization (MML) and 11 states now support recreational marijuana legalization (RML) (Cerda et al., 2020)

II. CANNABIS USE STATISTICS

A. Globally, 183 million people or 3.8 % of the adult population reported using cannabis in 2015 (Twardowski et al., 2019)

B. It is estimated the 22 million Americans over the age of 12 use cannabis every year (Alexander et al., 2019).

C. According to the National Institute of Health (NIH), cannabis use in 2015-2016 alone rose from 4.1% to 9.5% of the US population (Huson et al., 2018).

   i. Another recent study cited an increase from 7% in 2013 to 13% in 2016 (Horvath et al., 2019)

D. It is estimated that 10-20% of patients between 18 and 25 years regularly use marijuana

E. Cannabis remains the most commonly used illicit drug in the US (Alexander et al., 2019)

F. With growing legality, more patients are using cannabis and more patients are now willing to admit to cannabis use than in the past; this increases the likelihood that patients will be forthcoming during medical questioning (Twardowski et al., 2019).

III. PHARMACOLOGY

A. Marijuana is extracted from the dried leaves of the plant *C stiva* and contains approximately 450 distinct compounds, including 60 cannabinoids (Horvath et al., 2019)

i. Tetrahydrocannabinol, or THC, is typically present in the highest concentration but this varies by growing conditions (Horvath et al., 2019)

1. THC is primarily responsible for the psychoactive effects of cannabis, and therefore THC concentration is directly related to potency and efficacy (Horvath et al., 2019)

a. CBD does appear to attenuate THC's psychoactive effects (Horvath et al., 2019)

B. Two types of cannabinoid receptors; CB1 and CB2 (Horvath et al., 2019)

i. Cannabinoids act primarily via inhibition of adenylyl cyclase G-protein coupled receptors (Alexander et al., 2019; Horvath et al., 2019)

ii. CB1

1. Cannabinoid 1 receptors (CB1) are primarily expressed presynaptically in the peripheral nerves, spinal cord, basal ganglia, cerebellum, hippocampus, and association cortexes, but less so in the brain stem (Alexander, 2019; Horvath et al., 2019).

a. This distribution may account for the effects on nocioception, anxiolytics, memory, cognition, emotion, and movement with a relative sparing of respiratory depression (Alexander et al., 2019)

2. Low levels in the heart, blood vessels, peripheral autonomic neurons and other peripheral locations (Horvath et al., 2019)
3. Activation of CB 1 receptors results in inhibition of GABA, norepinephrine, dopamine, serotonin, and acetylcholine release and the indirect modulation of several other neuronal receptors, including opioid and NMDA receptors (Horvath et al., 2019)

iii. CB2

1. Cannabinoid-2 receptors are expressed primarily in immune and hematopoeitic systems where they have been shown to have inhibitory effects on inflammation, immune function, and nociception (Horvath et al., 2019)

iv. THC is a partial weak agonist at both, but some synthetic cannabinoids are full agonists at these receptors (Horvath et al., 2019)

v. However, the other hundreds of cannabinoids have variable effects; while some may be agonists of CB1 and CB2 like THC, other cannabinoids may act as antagonists or inverse agonists at one or both of the receptors (Alexander et al., 2019)

C. Pharmacokinetics

i. Pharmacokinetics are difficult to predict because THC concentration in any one delivered dose depends on several variables, including the THC concentration of the cannabis products, the route of delivery, and the metabolism and elimination of cannabinoids (Alexander et al., 2019)

ii. Cannabinoids are highly lipid soluble, so significant redistribution and accumulation occur once ingested. (Alexander et al., 2019; Echeverria-Villalobosa et al., 2019; Huson et al., 2018)

1. Inhalation
    a. THC and other cannabinoids are rapidly absorbed through the lungs with peak effects in 15 minutes. These effects can persist up to a dose-dependent 4 hours (Huson et al., 2018)
2. Oral ingestion
    a. Slower; peaks in 15-90 minutes but has a longer duration of action (approximately 5-6 hours) (Huson et al., 2018)
    b. Rapid first pass hepatic metabolism results in a blood concentration that is 25% of what occurs if smoked (Huson et al., 2018)
3. The cognitive and psychomotor effects can be present for up to 24 hours regardless of the route of administration (Huson et al., 2018).

iii. Plasma half life of THC ranges from 20 to 30 hours but the tissue half life may be as long as 30 days depending on the frequency and chronicity of use due to fat accumulation (Alexander et al., 2019; Huson et al., 2018; Horvath et al., 2019).

1. Therefore, the degree of intoxication cannot be predicted by laboratory studies (Alexander et al., 2019)

iv. Because of delayed elimination, drug interactions may occur up to 5 days after exposure (Echeverria-Villalobosa et al., 2019)

D. Metabolism

i. The liver is the major site of metabolism but the heart and lungs also contribute (Horvath et al., 2019)

1. THC has over 100 psychoactive and nonpsychoactive metabolites (Alexander et al., 2019; Horvath et al., 2019)

E. Elimination

i. Elimination of metabolites occurs via urine, bile, and feces (Alexander et al., 2019)

IV. PHYSIOLOGICAL EFFECTS

A. Cardiovascular

i. CV effects are mainly mediated by CB1 receptor stimulation.

1. This leads to activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system.
2. After 30 minutes of exposure, norepinephrine levels peak and stay elevated for up to 2 hours after cessation (Echeverría-Villalobos et al., 2019; Horvath et al., 2019).

ii. Various clinical studies have demonstrated that the initial tachycardia observed is mediated by adrenal release of epinephrine on beta adrenergic receptors along with parasympathetic inhibition.

1. Interestingly, pretreatment with propranolol effectively blocks this increase in heart rate, verifying that this effect is in fact mediated by beta adrenergic stimulation (Echeverría-Villalobos et al., 2019; Hudson et al., 2018)

iii. There is a dose dependent increase in systolic blood pressure and heart rate in naïve cannabis users immediately after beginning to smoke. In fact, once THC reaches its peak plasma concentration, there may be as much as a 20% to 100% increase in systolic blood pressure as compared to baseline values that can last up to 60 minutes after smoking cessation (Echeverría-Villalobos et al., 2019)

iv. Within the first hour of cannabis smoking, there is a 5 fold increased risk of myocardial infarction that rapidly decreases after the first hour of use. This elevated risk is thought to be due to a combination of tachycardia and peripheral vasodilation resulting in compensatory orthostatic hypotension and increase in CO, oxygen demand, and cardiac workload (Alexander et al., 2019; Horvath et al., 2019; Huson et al., 2018)

v. Ischemia stroke remains the most common vascular side effect in cannabis users. Recent studies have reported a 2.3-2.9 fold incidence of cerebrovascular ischemia in young cannabis smokers (25-35) when compared to tobacco smokers. One longitudinal cohort analysis demonstrated rates as high as 4.7 fold increased risk for ischemia stroke in cannabis users (Echeverría-Villalobos et al., 2019).

    1. Mechanism of cannabis induced stroke has been tied to cerebral vasospasm and atherosclerosis (Echeverría-Villalobos et al., 2019)

vi. As cannabis dosage becomes higher, a strong parasympathetic response ensues leading to bradycardia and hypotension (Echeverría-Villalobos et al., 2019; Huson et al., 2018). Deregulation of baroreceptors also occurs, meaning

that decreases in heart rate and postural hypotension are not able to be compensated for by sympathetic stimulation. When severe, cardiac arrest may occur (Echeverría-Villalobos et al., 2019)

vii. Whether cannabis is used recreationally or for medical purposes, its use has been associated with severe cardiovascular disorders such as malignant arrythmias, sudden on set a-fib, coronary spasm, sudden death, and cerebral hypoperfusion, and stroke. (Echeverría-Villalobos et al., 2019)

1. Cannabis has been linked to development of a-fib, a flutter, sinus bradycardia, and AV block (Huson et al., 2018)
2. In one study, males between 45-64 were identified to be at higher risk and a-fib was noted to be the most common arrhythmia reported in all age groups (Echeverría-Villalobos et al., 2019)

viii. Anesthetic considerations

1. Surgical stimulation causes SNS stimulation. THC may have synergistic cardiovascular effects when combined with surgical stress (Huson et al., 2018)
2. Much of the literature supports canceling general and regional anesthesia for elective surgery for 72 hours after the last exposure (Echeverría-Villalobos et al., 2019; Huson et al., 2018)
3. If surgery must proceed, all drugs that are known to effect heart rate should be avoided in patients with a history of acute marijuana use (Huson et al., 2018)
    a. Eg. Ketamine, pancuronium, atropine, and epinephrine

B. Respiratory

i. Unlike cigarettes, cannabis cigarettes tend to be unfiltered in nature. Because of this, there is approximately a 3 fold increase in tar inhalation and one third more tar deposition in the respiratory tract with cannabis versus cigarettes (Huson et al., 2018).

1. The tar produced by cannabis smoke also contains a greater concentration of two carcinogens (benzanthracenes and benzopyrenes) than tobacco (Huson et al., 2018). This means that cannabis plays a signifiant role in the development of lung cancers when chronically used.
2. Of note, one pooled analysis did find that infrequent smoking did not confer a greater risk of cancer after adjusting for cofounders (Huson et al., 2018).

ii. To maximize THC absorption, individuals take larger breaths and tend to hold it for longer periods of time. This results in 5 times the amount of carboxyhemoglobin levels as compared to the typical tobacco smoker (Huson et al., 2018)

iii. Due to the relatively high amount of carbon monoxide in marijuana compared to tobacco cigarettes, chronic marijuana smokers may be at higher risk of atheromatous disease (Alexander et al., 2019)

iv. Though laboratory studies consistently show that cannabis causes bronchodilation and decreased airway resistance mediated by CB1 receptors,

cannabis smoking still causes similar airway hyperreactivity as is seen with tobacco smoking (Huson et al., 2018).

1. One study estimated that 3-4 cannabis cigarettes daily is equivalent to about 20 tobacco cigarettes in terms of bronchial tissue damage (Huson et al., 2018)
2. In fact, because cannabis burns at a higher temperature than tobacco, it can actually be more irritating to the airways (Alexander et al., 2019).
3. Chemoreceptor and thermoreceptor stimulation via inhalation of cannabis can lead to laryngospasm, specifically during periods of lowered sensory afferent neuron threshold potentials such as during light anesthesia (Huson et al., 2019).
4. Heavy cannabis smoking can lead to goblet cell hyperplasia and increased secretions, loss of ciliated epithelium, uvular edema, and increases the risk of life threatening larygospasm during airway instrumentation (Huson et al., 2018)
5. A large cross sectional study with over 6000 patients found that the incidence of chronic bronchitis symptoms such as wheezing and productive cough occurred in cannabis patients 10 years earlier than tobacco smokers (Huson et al., 2018).

v. Perioperative respiratory evens such as reintubation, hypoventilation, hypoxemia, laryngospasm, bronchospasms, and aspiration are 70% more prevalent in smokers versus non-smokers (Huson et al., 2018)

vi. Anesthetic considerations

1. Because of the association of cannabis smoking with postoperative airway obstruction and pharyngeal/uvular edema, it is recommended to postpone surgery whenever possible if a patient has recently smoked (Echeverría-Villalobos et al., 2019).
    a. Much of the literature supports canceling surgery for 72 hours after last use (Echerverria- Villalobos et al., 2019; Horvath et al., 2019; Huson et al., 2018).
2. Administration of steroids in order to reduce uvular edema should be considered (Echerverria- Villalobos et al., 2019; Horvath et al., 2019).
    a. One study recommended 4-8 mg dexamethasone (Horvath et al., 2019); Another recommended 1 mg/kg of dexamethasone every 6-12 hours over the course of one to two days at the first sign of airway obstruction (Huson et al., 2018).
3. Albuterol, corticosteroids, and laryngeal topical anesthesia may all help to suppress cough and airway hyperreactivity (Horvath et al., 2019)
4. If volatile agents are going to be used, Sevoflurane may be the best choice since it is less pungent and associated with less coughing (Horvath et al., 2019)
5. Because of the increased risk of laryngospasm associated with smoking cannabis, deeper levels of anesthesia may be required to safely managed the patient's airway (Huson et al., 2018

C. Anesthetic medication interactions

i. Volatile anesthetic requirements.

1. Much of the literature supports increased volatile anesthetic use in chronic cannabis users (Echeverría-Villalobos, 2019; Holmen et al., 2020; Horvath et al. 2019)
2. One retrospective study assessing preoperative cannabis impact on intraoperative anesthetic delivery found that the average total volume of servoflurane administered was significantly higher among cannabis users.
    a. Cannabis users averaged of 37.4 mls versus non-smokers who used 25.0 ml of sevoflurane for the a tibial ORIF procedure (Holmen et al., 2020)

ii. IV anesthetics

1. One of the major mechanisms shared by general anesthetics and endocannabinoids is the modulation of GABA; therefore it's not unusual to see interactions between the two (Echeverría-Villalobos, 2019)
2. In chronic marijuana users, increased doses of propofol may be required for appropriate loss of consciousness as well as jaw relaxation and suppression of the airway reflex (Huson et al., 2018)
3. A study out of Colorado analyzed the dosages of fentanyl, Midazolam, and propofol required for an endoscopic procedure in cannabis versus non-cannabis users.

a. Cannabis users required 14% more fentanyl, 19.6% more Midazolam, and 220.5% more propofol as compared to non-smokers (Twardowski et al., 2019)..

iii. Opioids and acute pain management

1. Cannabinoids have been shown to be efficacious in the treatment of chronic neuropathic and cancer related pain; however cannabis appears to lower the pain threshold of surgical patients resulting in increased pain medication requirements in the postoperative period (Alexander et al., 2019;Horvath et al., 2019; Huson et al., 2018)
2. High dose cannabis use is associated with increased postoperative pain, additional doses of analgesics, and higher pain score in the immediate postoperative period compared to non-users (Horvath et al., 2019)
3. In one study, chronic cannabis users had a narcotic requirement that was twice that of the average patient of the same height and weight each day over the course of two postoperative days (Huson et al., 2018)
4. A multi-institutional pilot study found that marijuana use significantly affected acute pain management and resulted in increased consumption of opioid analgesics and greater self reported pain following traumatic injury (Salottolo et al., 2018)
5. 25-37% increase in opioid consumption for marijuana users than non users (Salottolo et al., 2018)

iv. NMBAs

1. THC depletes acetylcholine stores and exerts an anticholinergic effect; therefore, cannabis use may potentiate non depolarizing muscle relaxants (Huson et al., 2018)

v. Anesthetic considerations

1. Chronic cannabis users are likely to require more sedatives and volatile anesthetics as compared to non-smokers. This is something to consider for all patients, especially when doing offsite anesthesia where resources may be limited.
2. Though cannabis may be beneficial in treating chronic pain, chronic cannabis users are likely to report higher pain and require increased amounts of opioids in the postoperative period for acute surgical pain.
3. Monitor twitches and dose nondepolarizing muscle relaxants accordingly.

D. Gastrointestinal

i. THC consumption reduces gastric emptying time up to THC consumption reduces gastric emptying time for an average of 30 to 120 minutes placing these patients at higher risk for aspiration during airway instrumentation (Horvath et al., 2019)

ii. Cannabinoids Hyperemesis syndrome

1. Condition characterized by cyclic pattern of severe nausea and vomiting and abdominal pain in the setting of chronic cannabis use

2. Though the exact mechanism is still unknown, symptoms are likely mediated by CB1 receptor activity in the GIT or enteric nervous system (Echeverría-Villalobos et al., 2019)
    a. Chronic cannabis use can lead to downregulation of antiemetic CB1 receptors in the brain. This causes THC to turn from an agonist at these receptors to an antagonist (Echeverría-Villalobos et al., 2019)
    b. Its been hypothesized that reduced CB1 receptors may produce gastroparesis and subsequent triggering of hyperemesis (Echeverría-Villalobos et al., 2019)

iii. Anesthetic consideration

1. Consider utilizing preoperatively aspiration prophylaxis regimens to include H2-antagonist, proton pump inhibitors, and non-particulate antacids (Horvath et al., 2019)
2. General anesthesia should be induced using rapid sequence induction with cricoid pressure (Horvath et al., 2019)
3. There is currently no association between past medical history of cannabis hyperemesis syndrome and the risk of PONV with chronic cannabis users; therefore standard PONV recommendations apply (Echeverría-Villalobos et al., 2019)

E. Other effects

i. Cannabinoids can cause elevation in EEG activity that may render a BIS an unreliable marker of anesthetic depth (Alexander et al., 2019)

V. CONCLUSIONS

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