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Anesthetic Considerations For Patients Under The Influence Of Marijuana And/Or Cannabidiol: Anesthesia Interactions And Implications

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Abstract

This manuscript investigates the use of marijuana, including edibles and cannabidiol (CBD), and its effects on anesthesia. This topic of research is very recent without an abundance of information. Various articles discuss the route of marijuana use including inhalation, ingestible and extracts of the plant, including CBD. For this manuscript, the term marijuana will pertain to both inhaled and ingested marijuana unless otherwise noted; ingestible marijuana is also known as edibles. This manuscript explains the mechanism of action of marijuana and CBD, the general guidelines for the use and how each affect the administration and impact of anesthesia.

Keywords: marijuana, CBD, anesthesia

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Over the past five years, the legalization of marijuana has gained momentum throughout the United States. The legalization began with medical marijuana and has now progressed to recreational use; with this, brings an increased number of patients who chronically employ marijuana and its compounds. As of 2018, ten states and the District of Columbia have the widest-ranging laws and regulations regarding the recreational use of marijuana, while twenty-two other states authorized the use of medical marijuana ("Governing," 2018). The remaining states have yet to legalize either use of the drug. Marijuana, like other mind-altering substances, effects the body in a precise pharmacokinetic approach and can interact with anesthesia. This manuscript will explain what marijuana is, the different forms, compounds and routes marijuana can come in and how a patient's response to anesthesia may vary because of it.

Medicinal and recreational marijuana use has been an emerging trend for the past few years. There are many different viewpoints on the ethical, legal and societal ramifications of both applications. Bridgeman and Abazia (2017) discuss the history of marijuana throughout the centuries, the pharmacology behind the drug and how this could affect hospitals and surgical settings. The first documented use of marijuana was in 400 AD, however, in the United States it started to be utilized in the 1800s; since then marijuana has been federally restricted and controlled until most recently (Bridgeman and Abazia, 2017). Bridgeman and Abazia (2017) discuss both sides of the marijuana debate and acknowledge it is vital for them to be aware of the marijuana use in the general public and the effects it is beginning to have on the healthcare infrastructure.

Although there are multiple personal viewpoints and ideologies on the use of marijuana either recreationally or medicinally, it is a growing societal change and will continue to evolve rapidly. It is critical for providers to understand the pharmacodynamics and pharmacokinetics behind the use of marijuana and its chemical compounds. Whichever route or derivative of marijuana a patient uses, there is still potential for strong anesthetic interactions due to the metabolic enzymes and chronic side effects of the drug.

Pathophysiology of Marijuana and Cannabidiol

Bridgeman and Abazia (2017), state that the three most common methods for marijuana administration include inhalation by either smoking or vaporization, ingestion through edible products, and now CBD. Each of these methods varies based on the onset, intensity, and length of duration of the effects. Although smoking is the most common form of marijuana use, inhalation by vaporization is gaining popularity and may reduce the exposure of byproducts, carcinogens and decrease adverse respiratory effects (Bridgeman and Abazia, 2017). CBD can be given oral, rectal, sublingual or even transdermal (Bridgeman and Abazia, 2017).

Bridgeman and Abazia (2017) discuss endocannabinoids (eCBs) and their receptors found throughout the body. These receptors are in connective tissue, immune cells, the central nervous system, organs and glands (Bridgeman and Abazia, 2017). Until recently, it was not known what role the eCBs played a part of, and now they are thought to have a homeostasis role and function through the parasympathetic nervous system (Bridgeman and Abazia, 2017). A lack of eCB has been found to play a significant role in disease processes such as depression, fibromyalgia, irritable bowel syndrome, multiple sclerosis, schizophrenia and Parkinson's disease (Bridgeman and Abazia, 2017). Two of the most well-known eCB receptors include CB_1 and CB_2 (Bridgeman and Abazia, 2017). THC exerts its effects through CB_1 in the central nervous

system (Bridgeman and Abazia, 2017). Unlike THC, CBD does not attach to CB_1 and CB_2 receptors, but is thought to control endocannabinoid tone by hindering the uptake of the endocannabinoid anandamide, without any psychotropic effects (Morales et al., 2017). An anandamide is a neurotransmitter produced in the brain that binds to the THC receptors, and it is also known as the bliss molecule (Morales et al., 2017). CBD has the potential for use as an antiepileptic, anti-inflammatory, anxiolytic, antipsychotic and is said to have neuroprotective properties (Bridgeman and Abazia, 2017). GW Pharmaceuticals reported the very first conclusive results on CBD for the use in epilepsy in 2016 (Morales et al., 2017). There is no specific dose as of yet for the CBD dosage, but increased doses can cause sedation, and the medication should be started at lower doses and titrated up to either effect or presentation of side effects (Bridgeman and Abazia, 2017).

Marijuana's use in its natural state has been documented back 5,000 years; newer, synthetic derivatives are emerging for use in many different therapeutic modalities. Morales, Reggio, Jagerovic (2017) produced an overview of these more modern chemical compounds, their structure, and molecular targets. Marijuana exerts its effects over an endocannabinoid system (ECS), made up of CB_1 and CB_2 receptors as previously stated, and additionally of endogenous ligands, known as endocannabinoids (Morales et al., 2017). An endocannabinoid is a substance produced in the body that binds to cannabinoid receptors (Morales et al., 2017). The molecular targets of CBD are very complex and not well understood, but there are many hypotheses and little definitive proof (Morales et al., 2017). Anti-inflammatory and immunosuppressive effects of CBD have been shown to work through serotonin and adenosine receptors (Morales et al., 2017). CBD is useful for nausea and vomiting due to being a non-competitive $5HT_{3A}$ antagonist (Morales et al., 2017). Finally, CBD has shown to be a

transcriptional repressor and help to regulate cell proliferation and differentiation by DNA methylation (Morales et al., 2017).

CBD has not been extensively studied, although it has shown great promise for therapeutic uses; many research trials are ongoing regarding CBD. In future studies, the pharmacologic mechanism of CBD should be targeted so it can be directed at specific disease processes.

Literature Review

The articles utilized throughout this manuscript and within this literature review were found using the search engines PubMed, ResearchGate, Google Scholar and the US National Library of Medicine. The keywords utilized were: marijuana, CBD, edibles, and anesthesia.

Intravenous Delta-9-Tetrahydrocannabinol to Prevent Postoperative Nausea and Vomiting: A Randomized Controlled Trial

Delta-9-Tetrahydrocannabinol, also known as THC has been hypothesized to prevent a common side effect of anesthesia - postoperative nausea and vomiting (PONV). Kleine-Brueggeney, Greif, Brenneisen, Urwyler, Stueber, and Theiler (2015) conducted a randomized controlled study to evaluate if the utilization of intravenous (IV) THC could prevent PONV. This trial was a randomized, double-blind placebo-controlled study; Kleine-Brueggeney et al. (2015) hypothesized IV THC would diminish PONV by 25%. Forty patients were included in this study and received either a placebo or 0.125 mg/kg IV THC before emergence from anesthesia (Kleine-Brueggeney et al., 2015). The dominant outcome criterion was whether or not the patient experienced PONV within the first 24 hours after the administration of anesthesia (Kleine-Brueggeney et al., 2015).

The reduction in PONV was decreased by 12% in the group who received IV THC (Kleine-Brueggeney et al., 2015). Kleine-Brueggeney et al. (2015) found this not to be clinically significant as compared to other conventional PONV rescue treatments. Although PONV was decreased by IV THC, there were critical side effects experienced. These side effects include extreme sedation, increased confusion, mood swings, hallucinations and increased anxiety postoperatively (Kleine-Brueggeney et al., 2015). Kleine-Brueggeney et al. (2015) assumed that the peak effects of THC would be gone after emergence. However, their study showed that patients who had received IV THC took much longer to emerge from anesthesia, had increased sedation scores in the post-anesthesia care unit (PACU) and took statistically longer to discharge. Although IV THC is used in alternative settings, such as with chemotherapy-induced PONV, according to Kleine-Brueggeney et al. (2015), IV THC has no place in the perioperative setting at this time.

This randomized controlled trial has many limitations. Kleine-Brueggeney et al. (2015) stopped the study after their first analysis due to the untoward psychotropic effects IV THC was having and the minimal PONV reduction. Also, the dose chosen for this study was arbitrarily done based off of research for PONV induced by chemotherapy (Kleine-Brueggeney et al., 2015). There is currently no scientifically proven dose for THC in the treatment of PONV; 0.125 mg/kg is considered a larger dose. Therefore, it is possible that the side effects seen from IV THC were dose-dependent (Kleine-Brueggeney et al., 2015). Finally, Kleine-Brueggeney et al. (2015) administered the IV THC at the end of the surgery, before emergence from anesthesia. Hypothetically, if it had been administered before induction or directly after that, it is possible it would have had a more significant PONV reduction and decrease in unwanted side effects.

Postoperative Shivering Among Cannabis Users at a Public Hospital in Trinidad, West Indies

Although anesthesia provides terrific conditions for surgery, it is not without its side effects. As stated in the study mentioned above, PONV is a significant side effect of anesthesia, and in addition, shivering is often seen in the PACU. Sankar-Maharaj, Chen, and Hariharan (2018) conducted a study to test a hypothesis in which chronic marijuana users experience shivering post anesthesia more frequently and more severely than patients without marijuana use. This study was an observational study and consisted of two groups, marijuana users and non-marijuana users (Sankar-Maharaj et al., 2018). To decrease variability with each patient, each of these patients received general anesthesia and were given warmed isotonic fluids during the procedure (Sankar-Maharaj et al., 2018). A core body temperature was monitored every ten minutes throughout their time in the operating room (OR) and the PACU (Sankar-Maharaj et al., 2018). To assess their level of shivering, each patient had an assessor to monitor the patient in the PACU, rate their shivering on a scale from 0-3, document what treatment they received and if the therapy rectified the shivering (Sankar-Maharaj et al., 2018). Shivering is critical to prevent to decrease metabolic demand and post-anesthesia complications.

Sankar-Maharaj et al. (2018) included 55 patients in their study - a relatively small sample size. Of these, 25 were marijuana users, and 30 were reported non-marijuana users. Shivering was found to have an overall incidence of 36% - 40% of shivering occurred in the marijuana user group, while 33.3% occurred in the non-marijuana user group (Sankar-Maharaj et al., 2018). When the severity of the shivering was examined, marijuana users were observed to have a higher intensity (Sankar-Maharaj et al., 2018). Although the data Sankar-Maharaj et al.

(2018) could not obtain statistical significance, it establishes a baseline for future, more extensive studies to be conducted.

The most prominent limitation of this study is the small sample size. Sankar-Maharaj et al. (2018) acknowledged it was challenging to recruit patients into the study who would admit to using marijuana regularly, which contributed to the smaller sample size. Sankar-Maharaj et al. (2018) referenced an evidence-based clinical practice guideline which discusses Body Mass Index (BMI) as being a critical factor in a patient's temperature regulation. However, Sankar-Maharaj et al. (2018) did not collect data such as BMI or weight and height. Additionally, Sankar-Maharaj et al. (2018) could not measure current THC blood levels before entering the OR, thus contributing to variability as to whether THC levels interfered with the patient's thermogenic mechanisms.

Guidance for the Use of Medicinal Cannabis for the Prevention or Management of Nausea and Vomiting in Australia

In 2017, the Australian Government Department of Health published a "Guidance for the use of Medicinal Cannabis for the Prevention or Management of Nausea and Vomiting." This guideline discusses the management of nausea and vomiting and how medicinal marijuana can help, similar in topic to the study which Kleine-Brueggeney et al. (2015) conducted. This guideline explores recommendations, efficacy, specific doses and administration, as well as patients tolerance and withdrawal from medicinal marijuana ("Australian," 2017). This guidance does not specifically address medicinal marijuana use related to general anesthesia; this is due to the lack of research in this specific field, because of this, alternative research must be included to postulate marijuana's effects perioperatively. The guideline distinctly mentions medicinal cannabis for nausea and vomiting should only be used after traditional clinical guidelines have

been exhausted (“Australian,” 2017). As other studies have suggested, the pharmacokinetic and pharmacodynamic interactions of marijuana with other medications such as anesthesia, have been hypothesized but not yet proven (“Australian,” 2017).

This guideline recommends high THC medicinal marijuana for nausea and vomiting treatment, but only after current and legally approved anti-emetics have failed. Currently, there is no research or data to recommend an initial dose of medicinal marijuana. As stated previously, generally treatments should begin low and be titrated to efficacy, while trying to avoid potential adverse side effects (“Australian,” 2017). The Australian guideline explained the reason many research studies regarding medicinal marijuana for nausea and vomiting have remained small is due to the poor compliance of patients because of the adverse effects such as hallucinations, somnolence, and dizziness ("Australian," 2017). Due to insufficient data on the drug to drug interactions with medicinal marijuana, it is challenging to prescribe while not having a proven safety profile. Many types of medication are given during general anesthesia, without knowing how marijuana interacts with these medications, it should not be thought to be benign.

The Australian Government Department of Health explains their most substantial limitation to be the inability to provide information on dosing, dose-response for efficacy and dose-response for toxicity. Guidance for the use of medicinal marijuana in nausea and vomiting can only be given by broad overview and as a last resort. There is little research behind the therapeutic dosage of marijuana, and it cannot be supported for postoperative nausea and vomiting specific to anesthesia.

Additional Literature

In addition to the above-randomized control trials, research studies and overviews, many other resources will be used to analyze the effects of marijuana on anesthesia. The National

Institute on Drug Abuse (NIH) has a thorough overview of what marijuana is and its implications, answering many pressing questions most individual users may have. The Foundation for a Drug-Free World offers a course on marijuana named "The Truth About Marijuana" (n.d.); here they discuss potential short and long-term effects of marijuana. This resource offers a documentary on marijuana and the potential for being a gateway drug. This source has a bias towards not legalizing marijuana, and this has been noted. In 2010, Martin-Santos, Fagundo, Crippa, Atakan, and Bhattacharyya published "Neuroimaging in Cannabis Use: a systematic review of the literature," which examined neuroimaging while under the influence of marijuana. Martin-Santos' (2010) study contributes to research on the pharmacodynamics and mechanisms marijuana has on the brain. “Preoperative Marijuana Inhalation- an airway concern,” authored by Mallot et al. (1996) discusses the variety of respiratory disorders which marijuana can cause if used before the induction of anesthesia, most commonly uvular swelling. Finally, in “Patients on Party Drugs Undergoing Anesthesia,” Steadman and Birnbach (2003) discuss how critical it is for all anesthesia providers to know how illicit drugs and now legalized drugs, affect each type of anesthesia.

Discussion of the Literature Review

Each of these articles will add depth and context to how the use of marijuana will affect patients under the influence of general anesthesia. Common side effects of anesthesia include PONV and shivering; Kleine-Brueggeney et al. (2015) and Sankar-Maharaj et al. (2018) both discussed the impact of THC on each of these. Kleine-Brueggeney et al. (2015) found a positive correlation, but an adverse reaction in their study when THC was used to prevent PONV; the more THC utilized, the higher the unwanted side effects elicited. Similarly, Sankar-Maharaj et al. (2018) found with the more THC used by the patient before anesthesia, the higher the severity

of shivering. However, Kleine-Brueggeney et al. (2015) and Sankar-Maharaj et al. (2018) differ in their ultimate point of view. Kleine-Brueggeney et al. (2015) attempted to use THC to prevent a common side effect of anesthesia, while Sankar-Maharaj et al. (2018) believed the use of THC caused worsening of a common side effect of anesthesia. Kleine-Brueggeney et al. (2015) discussed that there is no proven dose for THC. Similarly, in their limitations "Australian" (2017) stated there is little research on the medicinal dosage of marijuana and their recommendations cannot support its use in PONV. However, "Australian" (2017) did not recommend the use of marijuana in the perioperative period due to its lack of a proven safety profile, whereas Kleine-Brueggeney et al. (2015) attempted the use of THC in the perioperative period and experienced negative adverse reactions.

The additional articles included within the literature review are similar to one another in the respect that each of them offers an essential aspect of how marijuana will affect anesthesia. The NIH overview provides a thorough and non-biased overview of marijuana. Similarly, the Foundation for a Drug-Free World also offers an overview on marijuana, but additionally discusses the negative impact in which it can have on individuals and has a biased undertone against the legalization and medicinal use. Martin-Santos et al. (2010) discussed the neuroimaging accomplished while marijuana users were under the influence and the mechanisms in which it affected the body; this data can be utilized to hypothesize how the effects of marijuana might affect patients under the control of anesthesia. Similar to Martin-Santos et al. (2010), Mallot et al. (1996), discussed the mechanisms in which marijuana affects the body. Both of these studies addressed the potential harm marijuana could bring to the different pharmacodynamic relationships and mechanisms within the body. Martin-Santos et al. (2010) and Mallot et al. (1996) differ in which areas of the body they were focusing; the research of

Martin-Santos et al. (2010) targeted marijuana's effects on the brain, while Mallot et al. (1996) focused on marijuana's effects on the airway.

Each article included in the literature review brings strengths and weaknesses to the research and offers an excellent background and baseline for future research to build a foundation.

A Systematic Review and Meta-Analysis

The Journal of the American Medical Association performed a systematic review and meta-analysis on the use of marijuana in the medical setting. Whiting, Wolff, Deshpande, Di Nisio, Duffy, Hernandez, Keurentjes, Lang, Misso, Ryder, Schmidlkofer, Westwood and Kleignen (2015) included 79 randomized trials with the use of marijuana or its derivative for the following indications: Tourette syndrome, PONV due to chemotherapy, chronic pain, depression, psychosis, multiple sclerosis, glaucoma, paraplegia spasticity, appetite stimulation, anxiety/sleep disorders and medication-induced adverse effects. Each study quality was examined by the Cochrane risk of bias tool, with the primary outcomes being activities of daily living, patient-relevant/disease-specific outcomes, and quality of life (Whiting et al., 2015). This systematic review and meta-analysis is critical to set a baseline for research on the medicinal use of marijuana going forward, as its use will become more common practice with the increased legalization.

The majority of the 79 trials and 6462 participants identified improvement in the primary outcomes. When given marijuana, patients were shown to decrease the incidence of chemotherapy-induced PONV from 47% to 20% (Whiting et al., 2015). Pain reduction decreased 6% and spasticity related to multiple sclerosis and paraplegia reduced as well (Whiting et al., 2015). Whiting et al. (2015) did find an increase in short term adverse effects with the use of

marijuana; these included drowsiness, hallucinations, dizziness, euphoria, confusion and dry mouth.

After evaluation of 79 randomized controlled trials, Whiting et al. (2015) concluded there was moderate evidence to support the use of marijuana in the treatment of chronic pain and spasticity related to multiple sclerosis and paraplegia. To a lesser extent, there are decreased quality studies to suggest marijuana use helpful in sleep disorders, Tourette syndrome, appetite stimulation and PONV related to chemotherapy (Whiting et al., 2015). As stated before and proven in this systematic review and meta-analysis, there is a lack of research on the implications of marijuana use and anesthesia.

Cannabis Consumption Before Surgery

Karam, Abbasi, and Khan (2015) published an article on the direct effects of chronic marijuana use and anesthesia. According to Karam et al. (2015) cannabis effects everybody system, specifically the central nervous system, respiratory system and cardiovascular system- each of which anesthesia also directly effects. Karam et al. (2015) state that minimal doses of marijuana increase sympathetic activity leading to tachycardia, but at the same time decreases the parasympathetic system, conversely depressing cardiac output. Alternatively, increased doses of marijuana inhibit the sympathetic system, which can lead to reduced blood pressure and bradycardia (Karam et al., 2015). What may be seen on an electrocardiogram (ECG) in a chronic marijuana user includes decreased voltage of P-waves, premature ventricular contractions (PVCs) and ST and T wave changes (Karam et al., 2015). The THC in marijuana synergistically affects medications which cause cardiac depression, thus leading to myocardial depression and myocardial infarction (Karam et al., 2015). Karam et al. (2015) state that the inhalation of marijuana can cause airway irritation and lead to upper airway edema, laryngospasm, and

bronchospasm. Sputum production has been noted to be 144% greater in marijuana smokers, as compared to non-smokers (Karam et al., 2015).

Karam et al. (2015) presented a case study in which a chronic marijuana user presented for surgery. Although this patient presented with tachycardia initially, they did not experience any untoward cardiac effects from their anesthetic. Karam et al. (2015) observed an increased need for opiates and hypothesized this might be due to the 20 years of chronic marijuana use.

Each patient and their marijuana use may differ, thus leading to significant variability in reliability for predicting their response to anesthesia. More careful studies and case reports are needed to correlate THC blood levels and anesthetic complications related to marijuana use.

With the increase in the use of marijuana due to the legalization, more patients are presenting to surgery with a history of continuous use. Richtig, Bosse, Arlt, and von Heymann (2015) present a case study in which a patient required increased doses of anesthetic medications to obtain an adequate level of anesthesia and analgesia. In this case study, the patient received extremely high doses of multiple drugs indicated for the induction of anesthesia with little to no effect. An anesthetic effect was finally achieved with a multi-modal approach. Richtig et al. (2015) hypothesized the reason for this unprecedented amount of medication is the interaction between the marijuana the patient chronically used and the anesthetic medications administered.

Richtig et al. (2015) recommend that patients with chronic marijuana use are carefully monitored for their depth of anesthesia and analgesia. Due to the inability to predict the interaction of marijuana and anesthesia, it is difficult to determine whether the patient will be able to achieve an adequate level of anesthesia for the surgery. Richtig et al. (2015) hypothesize THC and other compounds in the marijuana effect the gamma-aminobutyric acid (GABA) receptor and decrease the efficacy of its transmission; this would explain why propofol and other

anesthetic medications which work on inducing the GABA receptor failed to do so in their case study.

Although marijuana use has been studied extensively for medicinal use, there is minimal research to assess the use of marijuana and its effect on the patent perioperatively, specifically with anesthesia. Huson, Granados, and Rasko (2018) set out to observe the operational considerations for patients utilizing marijuana through a literature review. Huson et al. (2018) estimate that 10-20% of patients between the ages of 18-25 chronically use marijuana. Huson et al. (2018) included 263 studies in their literature review; it was found since there is little research on the specific topic, the researchers had to ascertain information from various fields of study regarding marijuana use. Huson et al. (2018) utilized the research found to answer the following four questions: (a) how is marijuana use assessed for in preoperative settings (b) what could be the potential complications during surgery from marijuana use (c) how should surgeons care for patients using marijuana during an elective surgery (d) does marijuana have the same effects as tobacco use.

Huson et al. (2018) found young chronic users of marijuana to have increased cardiac workload, an increase in the risk for myocardial infarctions and an increased incidence of strokes. The pulmonary complications associated with inhaling marijuana were found to be similar to that of a smoker; increased airway obstruction and reactive airways lead to anesthetic complications (Huson et al., 2018). Huson et al. (2018) found that anesthesia providers required an increased amount of medication to place a laryngeal mask airway (LMA). Huson et al. (2018) discussed a case report where three patients experienced respiratory distress; in all three cases, the patients inhaled marijuana within 6-12 hours before anesthesia. Marijuana-induced uvular edema, as described by Mallat, Roberson, and Brock-Utne (1996) is a potentially severe

postoperative complication, and a case should be canceled if the patient has acutely inhaled marijuana. Throughout the literature review, Huson et al. (2018) identified the potential for an increased incidence for laryngospasm. In multiple case reports, Huson et al. (2018) identified chronic marijuana users mandating increased boluses of propofol to achieve unconsciousness, sufficient relaxation and adequate blunting of the airway reflexes. Some of the effects of marijuana on anesthetic medications include: sensitization of the myocardium to catecholamines due to a higher level of epinephrine, increased duration of a nondepolarizing muscle relaxant, and potentiation of drugs which cause respiratory and cardiac depression (Huson et al., 2018). One article Huson et al. (2018) included discusses the potential to avoid all anesthesia in a patient who has utilized marijuana as recent as 72 hours prior. Patients with chronic marijuana use will have an unpredictable reaction to the anesthesia provided to them; due to the inability to predict the interactions between marijuana and drugs given during anesthesia, abstaining from the use of marijuana before surgery is recommended.

Huson et al. (2018) brought to light a significant concern for the use of marijuana and elective surgery. Many studies highlighted the effects marijuana has on the body and the multi-system involvement. Huson et al. (2018) discuss the potential for marijuana to affect the patient negatively throughout their operative period, whether it is used acutely or chronically. More current research needs to be conducted on the effects of marijuana and the present anesthetic medications available.

Implications of Recreational Drug Use

Beaulieu (2017) specifically addresses the interactions between recreational drugs such as marijuana and anesthetics. Beaulieu (2017) acknowledged with the increase in the use of recreational drugs it is undoubtedly inevitable to care for a patient under the influence of either

acute or chronic drug intoxication. Beaulieu (2017) states since drug use is so commonplace, it is critical for anesthesia providers to be aware of the common recreational drugs and how they present, their adverse effects and what anesthesia methods could help or harm the patient.

Patients can develop a tolerance to marijuana, even after only a few doses; patients who discontinue the use of marijuana will experience withdrawal (Beaulieu, 2017). This withdrawal can consist of irritability, restlessness, anxiety, depression, insomnia, weight loss or nausea (Beaulieu, 2017). The onset of this withdrawal will begin around two days post cessation and can continue up to one month, with a peak around one week (Beaulieu, 2017). When caring for a patient with either acute or chronic marijuana use, it is crucial to gather the time of their last dose, the amount and how often they use the drug (Beaulieu, 2017). Beaulieu (2017) explains that if the patient is acutely intoxicated with marijuana or another illicit drug and the surgery is not pressing, it is prudent to cancel.

Throughout the intraoperative period, Beaulieu (2017) outlines three areas for management of patients under the influence, and these include: (a) if the patient is acutely altered, manage their intoxication (b) prevent withdrawal (c) ensure a safe recovery and adequate analgesia (Beaulieu, 2017). Beaulieu (2017) discusses marijuana's effects on many different body systems but most importantly its impact on the respiratory, cardiac and central nervous system - each of which play a critical role in anesthesia. Similar to tobacco, inhaled marijuana will mimic the damage which will ensue (Beaulieu, 2017). Adverse effects to be anticipated in a regular marijuana smoker include airway reactivity, edema, obstruction and possible bronchospasm (Beaulieu, 2017). Beaulieu (2017) stated there is a five times increase in risk for myocardial infarction after the first hour of marijuana use due to the myocardial oxygen demand, increase in cardiac output, rise in catecholamine levels, increase in carboxyhemoglobin and

hypotension due to positioning. For acute marijuana use before general anesthesia, this may increase the anesthetic effects and prolong somnolence (Beaulieu, 2017). In a chronic marijuana user, increased doses of propofol are required for placement of an LMA (Beaulieu, 2017). Chronic users also have a more unpredictable response to medicines used for induction of anesthesia (Beaulieu, 2017). Marijuana is metabolized by CYP3A4 and CYP2C9, both part of the cytochrome P450 enzyme class (Beaulieu, 2017). Medications which are also metabolized by CYP2C9 are warfarin, Plavix, nonsteroidal anti-inflammatory drugs (NSAIDS) and Celebrex (Beaulieu, 2017). Additionally, medications metabolized by CYP3A4 consist of codeine, fentanyl, and oxycodone (Beaulieu, 2017). Due to the similar metabolism, there is an increased likelihood for an interaction between these medications and marijuana (Beaulieu, 2017). Beaulieu (2017) explains when marijuana is given with sedative drugs, such as many anesthesia medications, a higher level of drowsiness is seen. However, when presented with excitatory medicines such as amphetamines, marijuana provides an increased stimulant effect.

Marijuana is the most common recreational drug used nationwide and has a significant and unpredictable effect on anesthesia. It is vital for the anesthesia provider to know and anticipate how acute or chronic marijuana use may affect the patient, their presentation and their possible complications.

Cannabis Edibles

Another method of partaking in marijuana is to ingest the product. Ingestion of marijuana is most commonly known as edibles. Barrus, Capogrossi, Cates, Gourdet, Peiper, Novak, Lefever and Wiley (2016) explain edibles are generally considered a safe alternative to inhaling marijuana, as it does not cause the harmful effects to the respiratory system. The most significant difference between inhalational and ingestible marijuana is the delayed onset of effects (Barrus

et al., 2016). Currently, there is minimal research on therapeutic and subjective effects of edibles and the safety of this method (Barrus et al., 2016).

Edibles are consumable food products which have been mixed with cannabis extract; some examples include cookies, brownies, lozenges, and beverages (Barrus et al., 2016). Usage of edibles is increasing for three main reasons:

1. Ingesting marijuana is a more tactful and easy way
2. The high from edibles seems to be calmer
3. Edibles avoid harmful toxins seen with smoking marijuana (Barrus et al., 2016).

Research has neither confirmed nor denied any of these theories. Barrus et al. (2016) state ingesting edibles does not affect the respiratory function or increase the person's risk for cancer, however regular use of marijuana in either form does have adverse effects on the cardiac system, mental health and brain development (Barrus et al., 2016). Edibles are more readily associated with overconsumption than inhalation marijuana due to the delay in onset and impatience of users (Barrus et al., 2016). Edibles are metabolized through the gastrointestinal tract; from there THC is taken up into the bloodstream and travels to the liver through the portal vein (Barrus et al., 2016). In the liver, THC goes through the first pass effect through the cytochrome P450 system and is transformed into 11-hydroxytetrahydrocannabinol, a more potent psychotropic form than THC (Barrus et al., 2016); due to this, it is hypothesized edibles are stronger and longer lasting then inhaled marijuana.

Edible use has even less research and known effects than that of traditional inhaled marijuana (Barrus et al., 2016). There is no research relating edible use and anesthesia interactions, although it is hypothesized with the induction of the CYP450 system an increased dose of propofol and other medications may be necessary for adequate anesthesia.

Considerations for the Anesthesia Provider

Along with the United States, other countries, such as Canada are legalizing the use of marijuana in both recreational and medicinal capacities. Beaulieu, Boulanger, Desroches, and Clark (2016) discuss the medicinal regulations in Canada and how anesthesiologists may be able to utilize marijuana in their practice.

Throughout Canada, there are many different licensed producers which patients can register with and obtain their prescription for marijuana (Beaulieu et al., 2016). Due to the fact there are many producers of marijuana, there are also many different ratios of THC and CBD and minimal guidance as to what combination to prescribe to patients (Beaulieu et al., 2016). Chronic users of marijuana report using 1-3 grams of dried marijuana per week (Beaulieu et al., 2016). Beaulieu et al. (2016) included 26 clinical studies in which 13 used medicinal marijuana for neuropathic pain and the rest for other conditions including fibromyalgia, musculoskeletal disorders, and other chronic pain disorders. The Canadian health system published several recommended contraindications for marijuana use, these include: (a) below the age of 25 (b) pregnancy or breastfeeding (c) substance use disorder (d) severe respiratory or cardiac disease (e) individual or family medical history of mental disorders, including schizophrenia (Beaulieu et al., 2016). In addition, there are added conditions in which providers should use caution when prescribing medicinal marijuana including use of tobacco, mood/anxiety disorder, the risk for cardiovascular disease and consumption of large amounts of alcohol, narcotics or benzodiazepines (Beaulieu et al., 2016). Similar to other studies, there is no basic dosing range for marijuana, but use the mantra "start low and go slow" (Beaulieu et al., 2016).

The research behind medicinal marijuana plays an important role in preparing for the increase in recreational marijuana use. Beaulieu et al. (2016) found medicinal marijuana to be

most supportive for analgesia in chronic pain. Although therapeutic use of marijuana is becoming better understood every day, the risk-benefit ratio must be considered while prescribing this as an adjunct.

Psychiatric & Anesthetic Implications of Substance Abuse

The past decade has been devastated by substance abuse which spans all levels of social and economic barriers. Although marijuana has been legalized in many states, Bala, Kaur, Attri, Singh, Thakur, and Jain (2015) discuss the psychiatric and anesthetic implications of this drug and many others. Bala et al. (2015) define addiction as "compulsively seeking to use a substance, regardless of the potentially negative social, psychological, and physical consequences." The dependence on the drug can be either physical, mental or sometimes both.

Drug addiction although challenging to predict does have predisposing factors. Bala et al. (2015) explain drug use is seen more often in men aged 15-24 years, individuals who suffer from unemployment, peer pressure, alteration in lifestyle and of course, the easy accessibility to drugs. Marijuana, although considered generally safe, can still be abused. Bala et al. (2015) discuss how marijuana causes an increase in the sympathetic nervous system and a concurrent decrease in the parasympathetic nervous system; this can lead to tachycardia and an increase in cardiac output. Studies have shown a cross-tolerance between anesthetic medications used as adjuncts, including benzodiazepines, alcohol, barbiturates, and phenothiazines (Bala et al., 2015). Acute use of marijuana causes tachycardia. Therefore medications which increase the heart rate, such as ketamine, atropine, and epinephrine should be avoided (Bala et al., 2015). As stated in a previous study, marijuana causes a synergistic reaction with volatile anesthetics and can cause detrimental myocardial depression (Bala et al., 2015). These untoward reactions between marijuana and anesthesia can delay and impede recovery.

Although substance abuse is being fought on all levels, it is still a growing trend. It is essential to get a thorough history and physical to administer the best anesthetic and avoid potential complications.

Metabolism, Drug Interactions & Adverse Effects

The government of the District of Columbia, Department of Health published an overview of medicinal marijuana written by Fugh-Berman, Wood, Kogan, Abrams, Mathre, Robie, Raveendran, Onumah, Mehta, White, and Kasimu-Graham (n.d.). Fugh-Berman et al. (n.d.) discuss the general history of marijuana, the pharmacologic makeup and potential unwanted side effects and drug interactions.

Marijuana is a polypharmaceutical substance with over 108 cannabinoids, including THC and CBD, terpenoids and other chemical compounds (Fugh-Berman et al., n.d.). Administration of marijuana can be by inhalation or vaping, by mouth, sublingual and topical or rectal (Fugh-Berman et al., n.d.). Fugh-Berman et al. (n.d.) discuss that although there is minimal information on the safety profile of marijuana, severe reactions, such as death is rare. Common adverse effects seen with marijuana include anxiety, sedation, dry mouth, dysphoria, reddened eyes, reduced coordination and an altered sense of time (Fugh-Berman et al., n.d.). Cytochrome P450 enzymes are a class of enzymes for metabolism in the liver; this class is made up of more than 50 enzymes (Lynch, 2007). Both THC and CBD are metabolized by cytochrome P450 enzymes, more specifically CYP3A4 and CYP2C9 (Fugh-Berman et al., n.d.). Medications which inhibit CYP3A4 will increase THC levels, while drugs which induce this enzyme will decrease THC and CBD levels (Fugh-Berman et al., n.d.). CBD is also metabolized by the enzyme CYP2C19 (Fugh-Berman et al., n.d.). THC induces enzyme CYP1A2, and this can in theory decrease concentrations of certain medications such as naproxen, haloperidol, clozapine, cyclobenzaprine

and chlorpromazine (Fugh-Berman et al., n.d.). In contrast, CBD is an inhibitor of the enzymes CYP3A4 and CYP2D6; seeing as though CYP3A4 is responsible for the metabolism of many drugs, the use of CBD may increase blood concentrations of calcium channel blockers, benzodiazepines, cyclosporine's, antihistamines and some statins (Fugh-Berman et al., n.d.). The enzyme CYP2D6 metabolizes antidepressants which are commonly used. Therefore CBD can increase concentrations of SSRIs, beta blockers, narcotics and tricyclic antidepressants (Fugh-Berman et al., n.d.). Fugh-Berman et al. (n.d.) describe the documented marijuana drug interactions which include warfarin, alcohol, theophylline, and clobazam. THC and CBD will increase warfarin levels, and chronic use of marijuana increases INR (Fugh-Berman et al., n.d.). The use of alcohol along with THC will increase concentrations of THC blood levels (Fugh-Berman et al., n.d.). Inhaled marijuana will decrease theophylline levels (Fugh-Berman et al., n.d.). CBD used in epilepsy has shown to increase clobazam concentration levels (Fugh-Berman et al., n.d.). When marijuana is used in conjunction with central nervous system depressants such as alcohol, benzodiazepines, and barbiturates, there is a synergistic effect (Fugh-Berman et al., n.d.). However, in one relatively small study, marijuana did not show an increased effect when given with narcotics (Fugh-Berman et al., n.d.).

As stated previously, marijuana is a polypharmaceutical substance and also includes compounds such as carbon monoxide, nitrosamines, ammonia, acetaldehyde and types of tars (Fugh-Berman et al., n.d.). In addition to the inhalation of cigarette smoking, if marijuana is inhaled, the respiratory adverse effects are increased (Fugh-Berman et al., n.d.). If marijuana is vaporized and inhaled, as compared to smoking, less carbon monoxide is created (Fugh-Berman et al., n.d.). Fugh-Berman et al. (n.d.) did include a study which showed no increase in chronic obstructive pulmonary disease (COPD) when marijuana is inhaled chronically. In addition, a

meta-analysis of six studies from four countries which included over 2,000 cases showed minimal evidence in which marijuana increased lung cancer among chronic users (Fugh-Berman et al., n.d.). Although it is not clear as to whether marijuana increases the risk for pneumonia, THC does inhibit alveolar macrophage ability and replaces the cilia bronchial epithelium with enlarged mucus-secreting bronchial epithelial cells (Fugh-Berman et al., n.d.). Fugh-Berman et al. (n.d.) continue to discuss contamination likely in marijuana and the possible metabolic effects including cardiac and respiratory effects.

Marijuana is mostly well tolerated by individuals, but it is not without its adverse effects and necessity for regulation. Marijuana should not be used in the population of young adults, pregnancy and breastfeeding mothers (Fugh-Berman et al., n.d.). If a user is experiencing an acute psychosis, marijuana should not be given (Fugh-Berman et al., n.d.). With prolonged use, fetal or adolescent exposure to marijuana can cause adverse changes to their cognitive ability (Fugh-Berman et al., n.d.). The way marijuana is metabolized is a concern with specific drug concentrations and should be monitored carefully.

Conclusion

Anesthesia is a complex and diverse combination of many different medications to provide the patient with optimal amnesia and analgesia throughout a surgical process. Medicines which a patient may take daily can interact with these anesthetic medications, both either positively or negatively. Most of these interactions are known preoperatively and can be mitigated to provide the best and safest anesthetic possible. When patients engage acutely or chronically in drugs, which have not been adequately studied or understood by the medical community, it presents a level of difficulty and unpredictably. Research on inhaled marijuana is more abundant than either edibles or CBD. The research included in this manuscript supports the

theory inhaled marijuana increases the incidence of a reactive airway and the amount of medication needed to achieve an appropriate level of anesthesia, while edibles and CBD only do the latter. Despite the route of marijuana use, there are still other effects on the body as a whole, especially the cardiovascular system. It is critical for an anesthesia provider to assess the patients' route and frequency of marijuana use, whether it is acute, chronic or both and to amend their anesthetic care plan accordingly. As legalization of recreational marijuana use and medicinal marijuana grow throughout the country, anesthesia providers should modify their pre-anesthesia interview to include questions on marijuana use and educate themselves on the potential interactions and implications during the perioperative period.

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