Pediatric Anesthesia and Critical Care Journal 2023;11(1):8-15
doi:10.14587/paccj.2023.2

PACCJ

Implications of marijuana use prior to anesthetic care

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Keypoints

1. Marijuana's effects on the central nervous system include euphoria, altered cognition, memory dysfunction, and paranoia or even psychosis. Acute use may decrease perioperative anesthetic requirements while chronic administration may increase dose requirements.
2. The acute effects of marijuana on the cardiovascular system include increased cardiac output and reduced systemic vascular resistance that may result in hypotension, potentiated by intravenous or inhalational anesthetic agents. Data from adult anesthesia care have indicated a higher incidence of myocardial infarction following the use of cannabis products.
3. Marijuana inhalation may cause upper airway edema and increase airway reactivity thereby increasing the incidence of laryngospasm or bronchospasm.
4. Frequency of cannabis use (acute versus chronic effects) and the method of consumption mediate the physiological end-organ effects of cannabinoids and may warrant specific considerations when planning anesthetic care.

Abstract

Marijuana is classified as a Schedule I substance by the Drug Enforcement Administration (DEA). In recent years, many states have chosen to legalize marijuana for medical purposes. However, marijuana remains one of the most commonly abused illicit substances in the United States with the highest prevalence of use occurring in adolescents and young adults. The continued widespread use of marijuana increases the likelihood that patients may present for medical or anesthetic care while intoxicated. Although there is extensive literature pertaining to the pharmacology of marijuana and its end-organ effects, our current understanding of the interactions between marijuana and anesthetic agents is limited. We present a 16-year-old adolescent who had a recent history of marijuana use the morning prior to surgery. The physiologic end-organ effects of marijuana are reviewed, its potential interaction with intraoperative anesthetic care presented, and options for anesthetic care discussed.

Keywords

marijuana, cannabinoids, tetrahydrocannabinol (THC), cannabidiol (CBD)

Introduction

Marijuana is an illicit substance composed of the dried flowers and leaves of the Cannabis plant.[1] The physiologic effects of marijuana are largely caused by the naturally occurring compounds known as cannabinoids.[1] The primary cannabinoids found in marijuana are

tetrahydrocannabinol (THC) and cannabidiol (CBD). These compounds have a widespread impact on human physiology, with THC being the primary psychoactive component. Marijuana is usually rolled into a cigarette, smoked from a pipe, or added to food. Alternatively, the compounds found in marijuana can be concentrated into resins and oils. Concentrates are then smoked via vaporization devices (vaping).[2] The method and quantity of consumption, as well as the cannabinoid concentration, affects the bioavailability of cannabinoids and determines the onset, intensity, and duration of the drug's effects.[1–3] In addition to these naturally occurring, plant-derived products, there has been increased production and availability of synthetic cannabinoids. These are molecules designed to mimic the effects of THC. Synthetic cannabinoids target CB1 receptors in the brain. These receptors are responsible for the psychoactive effects of cannabis-derived THC.

In recent years, many states of the United States have legalized marijuana for recreational and medical purposes. Additionally, marijuana remains one of the most commonly abused illicit substances in the United States with the highest prevalence of use occurring in adolescents and young adults. The continued widespread use of marijuana increases the likelihood that patients may present for medical or anesthetic care while intoxicated. Although there is extensive literature pertaining to the pharmacology of marijuana and its end-organ effects, the current clinical information regarding the potential interactions between marijuana and anesthetic agents is limited. We present a 16-year-old adolescent with a history of marijuana use prior to anesthetic care. The primary physiologic effects of cannabinoids are discussed, previous reports of adverse perioperative effects of its use reviewed, and suggestions for clinical care in patients with a history of use presented.

Case Report

Review of this case and presentation in this format followed by guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was a 16-year-old adolescent who presented for cystoscopy/ureteroscopy with lithotripsy and indwelling stent replacement. Past history was significant for nephrolithiasis and a urinary tract infection resulting in abdominal and flank pain. The patient was admitted for pain management related to a 5 mm right-sided nephrolithiasis seen on computed tomography. The stone was passed, and the pain resolved; however, the patient had two subsequent returns to the emergency department (ED) after the initial admission for right-sided flank pain accompanied by nausea and vomiting. Ultrasound revealed mild right-sided hydronephrosis and ureteral dilation. A complete blood count and hepatic function panel were obtained in the ED and were within normal limits. Review of systems was positive for abdominal pain, nausea, vomiting, and dark urine. When asked about alcohol, tobacco, and recreational drug use, the patient denied the use of these substances during the surgical pre-operative interview. However, when asked about substance use a second time by the anesthesia team, the patient admitted to daily marijuana use and added that she had smoked marijuana that morning. Current home medications included naproxen as needed for pain, tamsulosin (0.4 mg daily), and ondansetron (as needed). In the preoperative surgical unit, the patient's blood pressure was 135/75 mmHg, heart rate was 81 beats/minute, oxygen saturation was 97% on room air, and temperature was 36.4 °C (97.6 °F). The patient was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. After pre-oxygenation, anesthesia was induced with midazolam (2 mg), propofol (3 mg/kg), and fentanyl (100 µg/kg). Bag-valve-mask ventilation was provided with oxygen and sevoflurane followed by placement of a laryngeal mask airway (LMA). Maintenance of anesthesia included sevoflurane (inspired concentration 2-4%) in air and oxygen. Vitals were stable throughout the procedure. The right-sided cystoscopy/ureteroscopy with lithotripsy and stent removal took approximately 60 minutes to complete. Blood loss was minimal and

intraoperative fluids included 600 mL of isotonic fluids. Dexamethasone (4 mg) and ondansetron (4 mg) were administered for postoperative nausea and vomiting prophylaxis. Following completion of the procedure, the patient was transferred to the post-anesthesia care unit in stable condition. After an uneventful recovery, the patient was discharged home the same day.

Discussion

Cannabinoids primarily exert their effects via cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). The CB receptors are adenylyl cyclase G-protein coupled receptors. CB1 is most abundant in the central and peripheral nervous systems, localized primarily at the presynaptic nerve terminal. Functionally, CB1 receptors inhibit neurotransmitter release, preventing excessive neuronal activity. Activation of the CB1 receptor leads to a decrease in cAMP production, resulting in diminished protein kinase A (PKA) activity. CB1-dependent reduction in PKA activity leads to inhibition of neurotransmitter release. Activation of CB1 receptors inhibits the release of several different neurotransmitters throughout the central and peripheral nervous system including GABA, glutamate, and norepinephrine. CB2 on the other hand is more abundant in lymphoid and hematopoietic tissue, as well as microglia of the nervous system. Expression of CB2 mRNA transcripts have also been identified in the spleen, thymus, bone marrow, and other immune related organs. The expression of CB2 receptors in these tissues explains the potential for immunosuppression following activation of CB2 receptors in lymphoid tissue.

THC and CBD are two of the most abundant cannabinoids found in marijuana and cannabinoid products. The CB1 and CB2 receptors, are the primary targets for THC, which produces the psychoactive effects of cannabis. CBD has anti-psychoactive effects that may moderate the CNS effects of THC. Considering the relatively extensive expression of CB1 and CB2 receptors throughout the body, marijuana and related compounds can have variable and widespread effects on end-organ physiology (Table 1).

Table 1. End-organ effects of marijuana and cannabis use

Organ system	Acute effects	Chronic effects
Cardiovascular	Tachycardia. Vasodilatation and hypotension. Orthostatic hypotension. Potential for coronary ischemia and acute myocardial infarction.	Accelerated atherosclerotic disease.
Pulmonary	Bronchodilation. Airway hyperreactivity and bronchospasm. Airway edema.	Chronic bronchitis. Emphysema and chronic lung disease.
Central nervous system	Anxiolysis, sedation, and euphoria. Anxiety, paranoia and psychosis. Dizziness and headache. Memory dysfunction. Analgesia.	Same as acute effects. Tolerance is noted with repetitive use so that higher doses are required.
Gastrointestinal	Anti-emetic and anti-nausea effects. Treatment of chronic abdominal pain.	Hyperemesis.
Endocrine.	Depressed thyroid function. Dysfunction of the hypothalamic-pituitary-gonadal axis. Blunting of sympathetic stress response and decreased catecholamine and cortisol release. Altered glucose homeostasis. Improvement in lipid profile.	Reduced female and male fertility. Increased risk of adverse pregnancy outcomes. Inhibition of milk production during lactation. Gynecomastia.

The physiologic effects of cannabinoids are varied, depending on the dose, whether there is acute or chronic ingestion, the route of entry into the body (oral ingestion, vaping, inhalation), and the primary components present (THC vs. CBD). Blood levels are not helpful during anesthetic care or to determine clinical effects, as there is rapid absorption into the brain from the bloodstream due to the lipophilic nature of THC.[4,5] Therefore, blood levels

do not correlate with brain concentrations and the clinical effects of these agents, making it impossible to relate plasma THC to level of intoxication.[5,6]

When considering the perioperative implications of cannabinoid use, the clinical impact may vary significantly based on whether use is acute or chronic as well as the specific agent used. During the preoperative examination, the patient should be questioned as to the chronicity of use, the most recent use, the route of administration, and the type of cannabis product used. Inquiry should be made regarding the use of other illicit substances. As time permits, preoperative drug screening may be indicated to further investigate concomitant use of other substances. Throughout this process, the patient should be informed that this information is required only to ensure the safe provision of anesthesia.

The acute effects on the CNS remain the most commonly recognized and cited effects of the cannabinoids and generally include euphoria, anxiolysis, and analgesia. These CNS effects are the most common effects which result in the illicit and medically indicated use of these agents. However, acute stimulatory effects can be seen with anxiety, acute psychosis, and agitation.[7] The potential for such stimulatory effects on the CNS are more common with repeated use or excessive doses, which are facilitated by the availability of novel organic extraction techniques that may lead to the rapid ingestion of extremely high doses.[8,9] These effects may increase the potential for emergence delirium or even acute psychosis following anesthetic care while the potential for tachycardia, hypertension, and fever may simulate other perioperative emergencies including malignant hyperthermia, drug ingestion, malignant neuroleptic syndrome, thyrotoxicosis or serotonin syndrome. There is even less information regarding the impact of cannabinoids on requirements for maintenance doses of anesthetic agents, although the limited anecdotal data postulates an increased dose requirement for volatile anesthetic agents.[10] These issues are further clouded by a clinical trial suggesting that specific cannabinoids may impact EEG activity, increasing the BIS reading thereby decreasing its reliability as a marker of the depth of anesthesia.[11]

In clinical practice, there has been a significant increased use of cannabinoids in the treatment of both acute and chronic pain in various clinical scenarios.[12] As with other clinical scenarios, there have been mixed results reported based on the type of pain, its duration (acute versus chronic), and the cannabinoid administered. In general, beneficial effects have been reported primarily in chronic pain with limited efficacy noted in acute pain scenarios. Perioperatively, the preliminary data suggest that cannabis users report higher pain scores, have fragmented sleep patterns, and have increased dose requirements for opioids once cannabinoid use is discontinued acutely following surgery.[13,14] As with other surgical interventions and especially in this patient population, the perioperative approach to analgesia should include early and aggressive use of regional anesthesia and a multi-modal systemic approach using acetaminophen, non-steroidal anti-inflammatory agents, and other non-opioid adjuncts as indicated.

Significant respiratory effects have also been noted, especially after the acute administration of cannabinoids and marijuana via the inhalational route. As with other agents with irritant effects on the upper airway, there have been anecdotal reports of edema and inflammation of upper airway structures including uvular edema that may result in upper airway obstruction or laryngospasm. These effects may be more common than with tobacco smoke as marijuana burns at a higher temperature.[15–17] The potential for these upper airway effects have led to some authorities to suggest postponement of elective surgery and anesthetic care in patients with recent inhalational use of cannabinoids. Intraoperative administration of corticosteroids (dexamethasone) may be indicated to limit inflammation, decrease upper airway edema, and attenuate airway hyperreactivity.

Acute and chronic cannabinoid inhalation (smoking) can impact perioperative airway reactivity with divergent effects that include both bronchodilation related to direct

effects of cannabinoids on smooth muscle and the potential for enhanced airway reactivity and bronchospasm. In general, clinical and animal studies show bronchodilation and lowered airway resistance with cannabinoids regardless of the route of administration (oral or inhaled).[18] Irritant effects from the inhalational intake of cannabinoids is similar to or greater than that noted with tobacco use. Given that the temperature at which marijuana burns is higher than tobacco, the irritant effects and potential for thermal injury on the upper and lower airway may be greater than that seen with tobacco use.[19,20]

In the cardiovascular system, acute marijuana intake results in acute physiological changes that can last for hours including an increase in heart rate, cardiac output, and supine blood pressure.[21] Additionally, an augmentation of orthostatic changes has also been noted due to changes in vagal and sympathetic tone. These concerns are magnified in the adult patient and those at risk for coronary ischemia. In the 1-2 hours following marijuana use, there is an abrupt increase (5-times) in the incidence of myocardial infarction related to increased myocardial oxygen consumption due to tachycardia coupled with decreased delivery due to shortened diastolic times and reduced peripheral vascular resistance with a decrease in diastolic blood pressure.[22,23] Vasodilatation is the result of decreased calcium influx (L-type calcium channels) or increased potassium efflux with decreased neurotransmitter release through the effect of cannabinoids (CB1 receptors) on the sympathetic nervous system. Cardiovascular effects from sympathetic stimulation include not only tachycardia, but the potential for arrhythmias. The increased risk of myocardial ischemia, arrhythmias, and tachycardia has led to the suggestion to delay anesthetic care until tachycardia resolves following acute cannabinoid intake. This is particularly important to consider in patients who admit to synthetic cannabinoid use in the pre-operative encounter, as there is an increased likelihood of fatal arrhythmias and myocardial infarctions when compared to non-synthetic cannabinoid use. Acute marijuana use has also been anecdotally associated with peripheral ischemia and the need for amputation, presenting like Buerger's disease and resulting in amputation for some users, while chronic use may accelerate atherosclerotic disease.[21] There is also anecdotal evidence of cerebral ischemia after marijuana use; however, the data are conflicting regarding the effects of marijuana on cerebral blood flow.[21]

Cannabinoids can also have physiologic effects throughout the GI tract. Acute marijuana intake has anti-emetic and anti-nausea effects, which has been used to treat nausea and vomiting in various clinical scenarios including chemotherapy.[24] Marijuana and the cannabinoids have also been anecdotally used in the treatment of symptoms of bowel motility disorders including abdominal pain and constipation, related to its antagonistic effects on visceral sensation.[25] However, chronic use may result in cannabis hyperemesis syndrome with nausea, vomiting and abdominal pain.[26] Although the anti-emetic effects may appear to have perioperative applications in the treatment of postoperative nausea and vomiting (PONV), no clinically significant effects or decrease in PONV were noted in patients given intravenous THC, while there was an increase in the incidence of adverse effects including postoperative confusion and sedation.[27]

Marijuana use can also have significant physiologic effects on the endocrine system.[28-34] Beneficial physiologic effects include improvements in lipid profiles following acute marijuana use in patients with systemic lupus erythematosus. However, studies in rodents have shown that acute marijuana intake decreases levels of TSH and thyroxine due to its effect on the hypothalamus. Marijuana use can also lead to alterations in the hypothalamic-pituitary-adrenal axis resulting in decreased cortisone release in response to stress.[28,29] Similarly, norepinephrine and epinephrine levels decrease with acute marijuana use.[30] Glucose metabolism seems to be impacted by marijuana intake as well, as marijuana users have been observed to have lower fasting glucose and insulin levels.[31] Chronic marijuana use is associated with dysfunction of the hypothalamic-pituitary-gonadal axis.[28] Although there are

conflicting data, marijuana use decreases testosterone levels acutely until tolerance develops when testosterone levels return to normal.[32] Chronic use can result in decreased growth hormone and a decreased sperm count. Chronic male users may also be predisposed to the development of gynecomastia. In females, several studies have demonstrated alterations in menstrual cycle hormones in response to cannabis use with one study reporting an increased risk of infertility.[33,34] Chronic marijuana use has also been linked to a variety of adverse pregnancy outcomes with transplacental passage to the fetus.[34] Exposed fetuses had been shown to have long term adverse outcomes including lower test scores, increased impulsiveness, and hyperactivity.[33] Marijuana use during breast feeding may inhibit milk production through its effect on prolactin.[34]

Both acute and chronic marijuana and cannabinoid use can have a significant impact on perioperative outcomes in pediatric patients. Expanded access to medicinal and recreational marijuana increases the likelihood that patients may present for medical or anesthetic care while intoxicated. During the preoperative history and physical examination, the patient should be questioned regarding acute or chronic use of marijuana and cannabinoids. The primary concerns for anesthetic care involves the impact of these agents on respiratory, cardiovascular, and CNS function. Acute inhalation may increase the risk of perioperative airway reactivity with an increased incidence of bronchospasm and laryngospasm. Acute cardiovascular effects include tachycardia and vasodilatation which may increase the incidence of coronary ischemia in at risk patients.

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