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Short Communication

Interactions Between Anesthetic Agents and Cannabis

Sharon Lui[1]* and Allen Fielding[2]

[1]*Oral and Maxillofacial Surgery, Temple University Hospital, Pennsylvania*

[2]*Associate Professor, Temple University Hospital, Pennsylvania*

***Corresponding Author:** Sharon Lui, Oral and Maxillofacial Surgery, Temple University Hospital, Pennsylvania.

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Introduction

Since 2007 there has been a consistent rise in the use of cannabis with data revealing an increased use of 10.4% to 13.3% from 2002 to 2015, according to the National Survey on Drug Use and Health (NSDUH). Today, there is an estimated 55 million (16.9%) Americans who currently use marijuana in 2022, according to the National Center for Drug Abuse Statistics [1]. Specifically, cannabis use is most prevalent in young adults (age 18-25 years) and among men, although there is a general increase in its use among both genders. A survey in 2016 reported the primary use for marijuana being recreational (89.5%), with only 10.5% Americans report using marijuana strictly for medical reasons [2]. The euphoric sensation of feeling "high", is the major reason for its recreational use, along with subjective reasons of helping to ease an individual's anxiety [3].

Biochemical and physiologic effects of marijuana

The mechanism by which cannabis causes euphoria is due to the interaction with the body's endocannabinoid system. The system consists of cannabinoid receptors throughout the central and peripheral nervous system. The two most commonly found receptors are G protein-coupled receptors, cannabinoid receptor type 1 (CB1) and type 2 (CB2) [3]. CB1 receptors are found primarily in the central nervous system (in cortex, basal ganglia, and cerebellum) as well as peripheral organs [4]. It is the target for the partial-agonist endogenous neurotransmitter, anandamide (AEA) and exogenous tetrahydrocannabinol (THC), the active agent in cannabis. CB2 receptors are in the immune system and gastrointestinal system and responsible for anti-inflammatory effects [5].

Acute and chronic effects of marijuana have been documented, specifically with relation to its effect on the lungs because smoking is the primary form of its distribution. There is speculation that delta-9-tetrahydrocannabiniol (THC) is a key contributor to pulmonary effects and consequences [6]. With regards to pulmonary effects, a clinical review, conducted by Tashkin and colleagues, observed the acute changes to lung function in healthy individuals who were given marijuana joints containing 10 and 20mg of THC [7]. Results revealed an onset of effects beginning at 5 minutes, with peak effect at 15 minutes, lasting for at least an hour after inhalation. A direct correlation between THC dosage and bronchodilation, as well as an increase in specific airway conductance above baseline, were also noted. The proposed pathophysiologic effect of bronchodilation is thought to be from the ability of THC to inhibit release of acetylcholine from parasympathetic nerves, therefore causing relaxation of smooth muscle tone of the airway [8].

In an alternative study, Tashkin and colleagues evaluated chronic respiratory symptoms in smokers (of both marijuana and tobacco users) [9]. For the purpose of this discussion, the relevant study was Taskin's evaluation of chronic respiratory symptoms in the 144 habitual smokers (reportedly using once a day for >5 years) that were examined in his study. It was reported that there was a greater prevalence of sputum production, chronic cough, and wheezing in chronic marijuana users, compared to non-smoking individuals.

Further studies conducted by researchers have attempted to determine a correlation between risk for lung cancer, impact on patients with pre-existing condition of asthma, and chronic effects on lung function. At this moment, there does not appear to be a consensus of the impact which long-term use of marijuana has on the mentioned scenarios. More studies will need to be conducted to better understand the influence which marijuana has over a long period of time. However, it can be agreed that use of smoking marijuana does result in increased symptoms of sputum production, chronic cough, wheezing, and bronchodilation [10].

Propofol

Propofol is a commonly used anesthetic for its hypnotic effects in both general induction and maintenance of anesthesia. It is a lipid emulsion primarily composed of soybean oil, glycerol, egg lectin, and small amounts of EDTA [11]. The mechanism of action for this sedative anesthetic is its inhibitory effects on the neurotransmitter gamma-aminobutyric acid (GABA) through the GABAA receptors in the brain [12]. This causes an increased duration of opening chloride channels, resulting in hyperpolarization of cell membranes. Propofol elicits various CNS, cardiovascular, and respiratory effects, with dose-dependent effects affecting the CNS and respiratory drive of the patient. It has an immediate onset, within 40 sec-

onds, and a duration of action of about 5-10 minutes. If given for monitored anesthesia, the dosage for adults is 0.5mg/kg over 3 to 5 minutes with an additional 10 -20 mg as needed.

As expected of its function, propofol diminishes cognitive function but also decreases cerebral blood flow, intracranial pressure, and consumption of cerebral oxygen [12]. Off-label uses of propofol include suppressing refractory status epilepticus, though rarely used for this reason, as well as its antiemetic properties, whose mechanism remains unknown. Aside from propofol's CNS effects, cardiovascular changes can also be appreciated when monitoring a patient's vitals during sedation. Propofol causes hypotension and decrease in myocardial contractility when administered because of its vasodilating properties causing relaxation of vascular smooth muscles. Reflex tachycardia may be appreciated prior to observation of reduced blood pressure and mean arterial pressure. Lastly, propofol causes dose-dependent depression of the respiratory drive and reduces ventilatory response to hypoxia. A greater induction dose of propofol will cause hypercapnia, eventually resulting in an apneic state for the patient. The mechanism by which propofol causes these respiratory changes remains unclear, however the overall dose-dependent changes to an individual's respiratory drive can be consistently expected, with hypoventilation, decrease in MAP, and depression of tidal volume [13].

Propofol is contraindicated with patients who are hypersensitive to soybean oil and egg phospholipid, as the anesthetic emulsion contains soybean oil and egg lecithin. Caution should also be taken for patients with lipid metabolism disorders, as administration of propofol may cause an increase in serum triglycerides [14].

There have been several studies reviewing the use of propofol for induction, in patients who have a history of marijuana use, undergoing endoscopy or insertion of laryngeal mask [15,16]. A case-study conducted by Imasogie and colleagues evaluated 318 individuals in an endoscopy clinic in London, Ontario, of which 151 individuals were self-reported cannabis users and 167 individuals denied any history of cannabis use [15]. Cannabis users were further subdivided based on frequency of use (daily, weekly, monthly, and occasional users). All participants underwent endoscopy with propofol anesthesia procedure, with dosage of propofol recorded as amount needed to achieve and maintain sedation, with no other specifics regarding depth of sedation mentioned. The conclusion from Imasogie and colleagues revealed that cannabis users, in general, required a higher dosage of propofol to achieve adequate sedation than participants with no history of cannabis use. Furthermore, daily cannabis users were observed to have had the highest dosage of propofol required for sedation (0.33 mg/kg/min ±0.24) verses non-cannabis users (0.18mg/kg/min ±0.11). Similarly, an alternative prospective study, conducted by Flisberg et al. evaluated 60 patients (30 cannabis users, using >1/week, and 30 non-users), who were all inducted using propofol for insertion of a laryngeal mask [28]. Adequate induction was determined with a BIS value of <60 (loss of consciousness and eyelid reflex). Results revealed a greater induction dose of propofol for group of cannabis users than group of non-users (314.0 ± 109.3 mg vs. 263.2 ± 69.5 mg, $p < 0.04$). Results were not statistically significant in this case; however it is important to note the overall general increase in propofol dose required for satisfactory anesthesia when taking into account an individual's social history use for marijuana.

Midazolam

Intravenous midazolam is another common anesthetic agent which can be used for induction or maintenance of anesthesia. It has a lipid-soluble property allowing it to have a fast onset of action of approximately 2 minutes following injection, with peak sedation occurring at 5-10 minutes. Midazolam is a useful anxiolytic and hypnotic agent, capable of causing anterograde amnesia, as well as having properties which allow it to act as an anticonvulsant and muscle relaxant. Its properties come from its ability to increase binding of GABA neurotransmitter to GABA receptor, thereby allowing greater influx of chloride ions. This in turn hyperpolarizes and inhibits neuron cells, allowing midazolam to function as a sedative agent [16].

Dosage of midazolam for induction is 0.15-0.40 mg/kg IV and for IV sedation is 0.05-0.15mg/kg with a recommended maximum cumulative dose of 10mg. At high doses, midazolam can cause respiratory depression, especially in combination with other benzodiazepines or fentanyl. Rapid administration may result in hypotension and tachycardia, and possibly thrombophlebitis, however not as common as when using diazepam. Caution should be taken, when administering midazolam, in patients with closed angle glaucoma and in situations of hypotension and shock [16]. It is also contraindicated with patients who have a history of autism, bipolar disorder, and psychosis [17].

The current literature regarding interaction of cannabis with midazolam is limited and conflicting. On the one hand there can be found studies stating that regular cannabis users vs non-users require a higher dosage of anesthetic agent, while other studies do not endorse any significant changes to dosage.

Diazepam

Diazepam, an anxiolytic benzodiazepine, works similarly at GABA receptors to increase conductance of chloride ions, causing a hyperpolarization at the site of neuron membranes and reducing neuronal excitability [18]. Unlike midazolam, diazepam is a long-acting benzodiazepine with a relatively fast onset of 1-5 minutes, and length of action of 12 hours or more. While diazepam produces a certain degree of anterograde amnesia, it causes less effects of mental impairment, compared to midazolam. Diazepam is digested by the enzyme CYP34A and CYP2C19 and, after undergoing hepatic biotransformation, is broken down into multiple active

metabolites, specifically desmethyldiazepam [19]. These active metabolites have an elimination half-life of up to 100 hours, thus contributing to the long-acting effects of diazepam. Adverse effects of diazepam can include modest respiratory depression, bradycardia, hypotension, ataxia, and confusion. It is contraindicated to use diazepam in patients with hepatic insufficiency, sleep apnea, myasthenia gravis, and those with severe respiratory deficiency.

Current literature does not provide data for interactions between marijuana and diazepam**.** However, we have observed the beneficial use of diazepam in an outpatient setting, with patients undergoing oral surgery procedures, and having "smoother sedations" without the need to frequently re-dose anesthetic agents. We suspect this is due to the long-acting effects of diazepam and its active metabolites that offer a prolonged sedation for cannabis users, which some evidence has shown require a higher anesthetic requirement. But, additional studies and research need to be done in order to come to a definitive conclusion and consensus regarding efficacy of diazepam's sedative effects on frequent cannabis users.

Ketamine

Ketamine, a rapid acting N-methyl-D-aspartate receptor antagonist, is a dissociative anesthetic drug that is commonly used for short procedural sedation and approved for induction for general anesthesia. It has a chemical structure similar to phencyclidine and has effects of blocking cortical awareness to external stimuli [20]. Ketamine is also unique in that it has partial agonistic effects on opiate mu-receptors that, in conjunction with fentanyl, aid in analgesic properties during sedation procedures. It is an effective adjunct to a surgeon's anesthetic plan as it has no undesirable respiratory depressive effects, dilates bronchioles, and maintains laryngeal tone and reflexes [21]. Though it does cause mild to moderate increase in cardiovascular system, by raising the heart rate and blood pressure, thus requiring a higher myocardial demand for oxygen, and should be used with discretion for patients with known coronary artery disease. Ketamine is most associated with side effects of nausea, vomiting, confusion, dizziness, particularly dysphoria and an "out-of-body" sensation. However, regarding the association between use of ketamine and emergence delirium, there does not appear to be significant evidence supporting this connection. A prospective observational study was conducted in Portugal observing 115 patients undergoing laparoscopic surgery with the use of 0.5mg/kg ketamine intraoperatively (after induction with propofol) and the presence or absence of postoperative emergence delirium [22]. Of the 115 subjects, 60 patients were administered ketamine while the remaining 55 were not. 17 of the 115 subjects experienced postoperative emergence delirium, 11 patients were administered ketamine and 6 patients were not. The authors therefore concluded that there was no association between administration of ketamine for laparoscopic surgery and emergence delirium. Similarly, a prospective study of 745 pediatric patients, in the setting of the ED, was conducted to evaluate whether ketamine causes frequent emergence delirium in the younger population [23]. The results showed that 2.1% of the population experienced emergence delirium, with patients settling within 20 minutes. Though the distressing emergence is not preferred, there did not appear to be significant evidence deterring physicians from using ketamine as a means of sedation for the pediatric population, in the ED setting, with concerns for emergence delirium.

Ketamine has a quick onset of 20-30 sec. after an initial induction dose of 2mg/kg, with a duration of 20-30 minutes. Small boluses of 0.5mg/kg can be subsequently administered for maintenance and prolonged anesthesia may be observed from its active metabolite, norketamine [24]. It is prudent to understand that when given in high doses, in association with other respiratory depressive agents, the protective airway effects of ketamine can be lost, and respiratory depression can be magnified in these instances.

Regarding the interaction of ketamine and marijuana, the literature remains scarce with no reports suggesting modification in dosage when treating patients who are regular marijuana users. It is interesting to note that the analgesic effects of ketamine on NMDA receptors can aid with regulating analgesic effects for marijuana users, as these patients are prone to hyperalgesia [25]. It is also suggested that there may be a greater chance for emergence delirium, given the ketamine-marijuana combination. Therefore, use of benzodiazepines may aid in attenuating this scenario, should it occur [26].

Conclusion

There is an increasing use of cannabis that can be seen across the States, specifically in young male adults (18-25 years), meaning the occurrence of treating patients with a history of marijuana will continue to rise in the oral surgery setting. Understanding the base effects of marijuana on patients and the implications of continued substance use will better allow the clinician to formulate his or her anesthetic plan for patients undergoing deep/general anesthesia. Though the literature regarding interaction of cannabis and anesthetic agents is sparse, there is evidence that an overall higher dosage of sedation medications may need to be administered to marijuana users to achieve a plane of sedation appropriate for the said procedure to be performed [27]. There is a lack of comparison between the interaction of benzodiazepine and marijuana and further studies evaluating whether there is a superior use of midazolam verses diazepam for regular marijuana users. Despite the scarce evidence, we have observed the potential benefits of diazepam as the choice of benzodiazepine over midazolam for this specific population type. The reasoning behind this hypothesis is the long-acting effects diazepam has, because of its active metabolites. This is not to form a definitive conclusion, but to simply postulate that further studies need to be conducted to determine whether there is a more effective choice of benzodiazepine to be used for

patients with a history of marijuana use**.** Overall, it is important for the clinician to bear in mind the interactions which marijuana can have when sedating a patient, to ensure the safest and most optimal care delivered.

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