The American Journal of Surgery 217 (2019) 783–786

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Review

Impact of recreational and medicinal marijuana on surgical patients: A review

Chetna Bakshi [a], Allison M. Barrett [b, *]

[a] Resident in General Surgery, Department of Surgery, North Shore University Hospital, 300 Community Drive, Manhasset, NY, 11030, USA
[b] Penn State Health St. Joseph's Medical Center, 2494 Bernville Road, Reading, PA, 19605, USA

ARTICLE INFO

Article history:
Received 10 August 2018
Received in revised form
30 September 2018
Accepted 12 October 2018

Keywords:
Cannabis
Cannabinoids
THC
Marijuana
CBD

ABSTRACT

Background: As medicinal and recreational marijuana use broadens across the United States, knowledge of its effects on the body will become increasingly important to all health care providers, including surgeons.
Data sources: We performed a literature review of Pubmed for articles discussing the basic science related to cannabinoids, as well as articles regarding cannabinoid medications, and cannabis use in surgical patients.
Conclusions: The primary components in the cannabis plant, tetrahydrocannabinol (THC) and cannabidiol (CBD), have been made available in numerous forms and formulations to treat multiple medical conditions, and recreational access to marijuana is increasing. Of particular importance to the surgeon may be their effects on prolonging intestinal motility, decreasing inflammation, increasing hunger, mitigating pain, and reducing nausea and vomiting. Perioperative use of medicinal or recreational marijuana will become increasingly prevalent, and the surgeon should be aware of the positive and negative effects of these cannabinoids.

Introduction

As medicinal and recreational marijuana use expands across the United States, knowledge of its effects on the body will become increasingly important to all physicians, including surgeons. The literature on the effects of the cannabis plant, its active component tetrahydrocannabinol (THC), and other cannabinoids is expanding, highlighting the wide-reaching implications of the endocannabinoid system on the entire body. These properties are important for surgeons, who should be aware of the effects of cannabinoids on intestinal motility and secretion, inflammation, and hunger signals, as well as pain, nausea, and vomiting.

The basic science of cannabinoids

Cannabis is a commonly used psychoactive substance. While the cannabis plant contains numerous substances, the psychoactive properties of cannabis are largely thought to be secondary to tetrahydrocannabinol, or THC.[1] Cannabidiol (CBD) was historically less desirable in inhaled cannabis, but has proven to be useful for medical indications.

Cannabinoids bind to and serve a partial agonist for two types of G-coupled cannabinoid receptors, called cannabinoid receptor type 1 (CB1) and type 2 (CB2). Cannabinoid receptors are found throughout the body, including in tissues in the brain and gastrointestinal tract. Receptor CB1 is widespread, but is found in highest concentrations in brain and nervous system tissue, and lower concentrations in liver, adipose tissue, and vascular endothelium. Receptor CB2 is more strongly expressed in immune tissues and some neurons.[2,3] These receptors play a role in multiple pathways, including neuronal development and energy metabolism.

In most models, activation of cannabinoid receptors leads to inhibition of adenylyl cyclase and reduction in cyclic AMP, which is responsible for activation of protein kinase A (PKA). As PKA is involved in gene transcription, it may be hypothesized that activation of CB1 may result in decreased gene expression.[2]

THC activates CB1 receptors in the brain, which releases dopamine and results in the positive reinforcement often seen with drugs of abuse.[4] With prolonged exposure, cannabinoid receptors can become down-regulated and desensitized to variable degrees

* Corresponding author.
E-mail addresses: chetna.bakshi@gmail.com (C. Bakshi), amb809@gmail.com (A.M. Barrett).

https://doi.org/10.1016/j.amjsurg.2018.10.053
0002-9610/

in different tissues, in a dose-dependent manner.[5]

Subcutaneous and omental adipose tissues can show increased expression of CB1 in patients with obesity, which may contribute in part to hypothalamic function with respect to food intake. In obesity, the CB1 system is upregulated, both in the central nervous system and the periphery.[6]

Additional receptors for cannabinoids have been suggested. G-protein coupled receptor GPR55 shows some similarity to CB1 and CB2, but lacks the same ligand binding sites. Cannabinoids have been found to modulate its activity by other mechanisms. Peroxisome proliferator-activated receptor (PPAR) has also been found to have some cross reactivity, as CB agonists have also been found to be PPAR agonists.[7]

Cannabinoids and inflammation

Inflammatory conditions induced in murine models result in upregulation of CB1 receptors.[9] In addition, expression of CB2 and PPAR receptors are increased in the submucosa during inflammatory states. In murine colitis, reduction in inflammation can be seen with CB1 or CB2 receptor agonists, as well as agonists of PPAR and GPR55. According to Couch et al., cannabinoids have been found to have a dose-dependent effect on local inflammatory processes, including COX2 activation, cytokine expression, caspase 3 production, and enteric glial cell expression. Through these mechanisms, cannabinoids have been shown to be effective in reducing inflammation in murine models of experimentally induced colitis.[8]

Both CB1 and CB2 receptors can be found on natural killer and mast cells, as well as B cells in the gut. Cannabinoids inhibit the secretion of proinflammatory cytokines IL6, IL8, and TNF-alpha, as well as activated macrophages and mast cells. It is thought that CB activation thereby has a protective effect on inflamed intestines.[10,24]

The anti-inflammatory properties of cannabinoids may prove to be beneficial for patients with inflammatory bowel disease such as Crohn's Disease or ulcerative colitis, as well as those with rheumatologic conditions like psoriasis or rheumatoid arthritis.

Cannabinoids and intestinal motility

Multiple studies demonstrate that cannabinoids inhibit gastrointestinal motility. Murine models demonstrate that CB1 agonists result in inhibition of upper gastrointestinal tract motility[23] as well as colonic propulsion.[11] Keenan et al. studied the effect of AM841, an irreversible CB1 agonist, in mice and found it to reduce GI motility in both small and large intestine *in vivo*. This effect was more potent under stress where accelerated GI motility was normalized with AM841. This effect took place at a lower dose in the colon than in the small intestine.[12] Similarly, Troy-Fioramonti et al. showed that anandamide, an endogenous cannabinoid receptor ligand, slowed GI motility, and this effect was reversed by pre-treating mice with a CB1 and CB2 antagonists.[13] Likewise, whole gut transit time was found to be slower after synthetic cannabinoid agonist activation of the GPR55 receptor.[14]

The inhibitory effects on GI motility seen with CB agonists are due to the inhibition of excitatory neurotransmitter release in neurons found in the myenteric plexus. This in turn can lead to reduced peristalsis throughout the bowel. Similarly, CB1 antagonists have been shown to increase neural network activity thereby increasing GI motility.[15] This effect has been demonstrated with use of dronabinol (brand name Marinol), which has been shown to slow gastric and colonic motility, with little effect on small intestinal motility.[12]

Overall, cannabinoids results in slower gastrointestinal motility. This may be beneficial for patients with diarrhea-predominant irritable bowel syndrome and short gut syndrome.

Cannabinoids and intestinal secretion

Activation of CB1 receptors has been found to decrease gastric acid production through action on vagal pathways via acetylcholine. In addition, CB1 activation has been shown to be gastroprotective.[9] Both *in vitro* and *in vivo* studies suggest that CB1 receptor activation with synthetic compounds or plant extracts that are rich in THC decrease gastric acid secretion.[16] In addition to reducing gastric acid secretion, cannabinoids have been found to cause a transient relaxation in the lower esophageal sphincter, while mitigating mucosal damage and inflammation seen in GERD.[14]

These properties of cannabinoids may have relevance in treating patients with chronic ulcer disease, gastrinomas, or malignant bowel obstructions. Use of cannabinoids also may be protective against ulcer formation, for example, in patients who have undergone partial gastrectomy with gastrojejunostomy. It remains to be seen if smoking marijuana would have similar effects on acid secretion, as the data on smoking cigarettes is shown to increase ulcer risk.

Cannabinoids and hunger/satiety

The CB1 receptor plays a role in energy homeostasis. CB1 agonists can increase appetite thereby stimulating feeding, whereas antagonists suppress hunger leading to decreased feeding. Malfunction of the endocannabinoid system has also been linked to overeating and obesity.[17] According to Gotfried et al., the endocannabinoid system can induce hunger signals and hyperphagia.[14] This mechanism of action is via CB1 receptors in the limbic forebrain. Agonists of CB1 receptors stimulate appetite, whereas antagonists inhibit appetite. Endocannabinoids anandamide and 2-AG have been found to be elevated during fasting and decreased during eating.[18]

In addition to increasing appetite, CB1 receptors have been found to be involved in restricting energy expenditure. Antagonism of CB1 receptors resulted in enhanced thermogenesis and simulated heat production. Antagonism of CB1 receptors also has been suggested to enhance lipolysis, reduce eating, and decrease body mass.[18]

These properties of cannabinoids are relevant in the setting of AIDS- or cancer-related cachexia, where lack of appetite can be treated with cannabinoids. This has also been an intervention point in the past for pharmacotherapy for obesity, which will be discussed again later.

Cannabinoids and nausea/vomiting

The effect of cannabinoids in reducing nausea and vomiting is widely known. Cancer patients undergoing chemotherapy have long been aware of these effects. A Cochrane review in 2015 concluded that cannabis-based medications were useful for treating refractory chemotherapy-induced nausea and vomiting, but cautioned that data is mixed due to variability in regimens and protocols.[19]

It can be hypothesized that surgical patients at high risk for postoperative nausea and vomiting (PONV) may benefit from cannabinoids as well. However, one study from Levin et al. did not support that. A one-time preoperative dose of nabilone (brand name: Cesamet) did not have any effect on the incidence of PONV.[20] Additional research is needed regarding the possible role of perioperative cannabinoids in the management of PONV.

Cannabinoids and pain

The body of data regarding use of cannabinoids for pain management is extensive and will be mentioned only briefly here, as it relates to surgery. Research has pointed to the possible advantageous effect of co-administration of cannabinoids with opiates, resulting in reduced narcotic requirement.[21] Nielsen et al. performed a systematic review of the literature on opioid and THC administration and found that the effective dose of morphine was 3.6 times lower in animal subjects who received THC concomitantly. In the setting of multimodal pain management and a national emphasis on opiate-sparing techniques, this may be of value in the future. Additional research is needed regarding the possible role of perioperative cannabinoids in the management of acute postoperative pain, as human studies have only researched cannabinoids for chronic, non-surgical pain conditions, such as multiple sclerosis and end-stage malignancy.

Administration of cannabinoids

The cannabis plant has two main subspecies. The *Cannabis indica* dominant strains contain higher CBD concentrations, while *Cannabis sativa* dominant strains contain higher THC concentrations. Hemp, a strain of cannabis sativa, has a lower THC concentration than other strains, and was historically grown for industrial purposes. Smoked cannabis or vaporized THC results in detectable plasma concentrations within minutes of use, and resolution of effects in 2–3 h. Oral ingestion of THC and CBD undergoes first-pass metabolism in the liver, therefore results in less bioavailability. With oral ingestion, effects are seen within 30–90 min, with resolution of effects in 4–12 h.[22]

Medical marijuana dispensaries sell products in multiple forms with variable constitutions. Ingested forms are described as being “CBD Dominant” or “THC Dominant” and specific product information includes a ratio of THC-to-CBD. CBD-dominant products contain minimal THC to avoid its psychoactive and cognitive effects. These products are used for conditions such as epilepsy and Parkinson's disease, and in topical form for dermatologic or muscle/joint conditions. THC-dominant products result in more psychoactive and cognitive effects, and may be better suited for patients with conditions such as chemotherapy-associated nausea and vomiting, chronic pain, and AIDS.

Products come in the form of oil for vaporization, capsule, oral solution, or topical form, as well as edible products.

Cannabinoid medications

Many studies have been done to investigate the use of CB agonist and antagonist medications in treating a wide variety of conditions. However, given the presence of centrally located CB receptors, many of these medications have undesirable side effects. One CB1-antagonist was developed and marketed in Europe in 2006 as an “anti-obesity” drug. The purpose of Rimonabant (also known as SR141716) was to utilize the anorectic properties of CB1-antagonism to induce appetite suppression. It was approved for patients with BMI>30 or BMI>27 with comorbidities. The drug was withdrawn from the market within 2 years due to serious psychiatric consequences, with up to 10% of patients reporting depression, and 1% with suicidal ideation [25,26].

The U.S. federal government allows for formal prescription of three cannabinoid medications. Marinol and Syndros (generic name: dronabinol) are synthetic forms of THC that are approved by the FDA for loss of appetite due to AIDS, as well as chemotherapy and postoperative nausea/vomiting.[16] Cesamet (generic name: nabilone) is a synthetic cannabinoid that mimics THC. It is indicated for chemotherapy-induced nausea and vomiting.

Sativex, or nabiximols, a sublingual spray comprised of THC and CBD, was approved in the UK for use in multiple sclerosis for treatment of pain and spasticity. It is not available in the United States.

Marijuana use in the surgical patient

There is very limited data on the use of recreational marijuana in surgical patients. In the existing literature, marijuana use is self-reported and not quantifiable, limiting the utility of the available information. In one study of orthopedic surgery patients, those who were identified as having marijuana use disorder were found to have lower in-hospital mortality rates, but higher rates of heart disease, stroke, and coronary artery disease.[27]

The side effects of marijuana must be considered in surgical patients. We recommend that it should be a standard part of history taking to ask patients if they use marijuana. Especially in surgical patients, it may have implications on anesthesia, including cardiopulmonary effects.[28] In addition, patients undergoing bariatric surgery should be especially cautioned, as marijuana use could

Table 1
List of States in Which Recreational and Medical Marijuana are Legal (as of 6/25/2018).

Medical Marijuana Legal (in some form)	Recreational Marijuana Legal
Alaska	Alaska
Arizona	California
Arkansas	Colorado
California	Maine
Colorado	Massachusetts
Connecticut	Nevada
Delaware	Oregon
Florida	Vermont
Georgia	Washington
Hawaii	Washington DC
Illinois	
Indiana	
Iowa	
Kentucky	
Louisiana	
Maine	
Maryland	
Massachusetts	
Michigan	
Minnesota	
Mississippi	
Missouri	
Montana	
Nevada	
New Hampshire	
New Jersey	
New Mexico	
New York	
North Carolina	
North Dakota	
Ohio	
Oklahoma	
Oregon	
Pennsylvania	
Rhode Island	
South Carolina	
Tennessee	
Texas	
Utah	
Vermont	
Virginia	
Washington	
West Virginia	
Wisconsin	
Wyoming	

have negative effects on their eating habits and weight loss.[29]

Although there is insufficient current literature on the subject, it is important to consider marijuana's effects on inflammation and gut motility especially in colorectal surgery. Additional research is needed to determine the effects of marijuana in the surgical patient, and data is likely to become more available as recreational and medicinal marijuana use becomes legal in more states.

Availability of cannabinoids

State laws vary regarding the legality of recreational and medical cannabis use (Table 1). For recreational use, laws vary on the amount of marijuana an individual may possess at a given time. Medical marijuana laws also vary, with some states providing strict restrictions on the indications for use (i.e. terminally ill patients only) as well as the level of THC permitted in the product. Patients seeking medical marijuana must visit a specific licensed provider for a prescription, then go to a dispensary to obtain the products. On a federal level, recreational marijuana use remains illegal.

Conclusion

Cannabinoids including THC and CBD have widespread effects on the body. These effects are particularly notable in the intestinal tract, where cannabinoids slow down intestinal transit, reduce inflammation, and reduce gastric acid secretion. Other systemic effects include increasing appetite, reducing nausea and vomiting, and potentiating the effects of opioids on pain. There are numerous directions for cannabinoid-based pharmacotherapy in the future, and we are likely to see this evolve over the coming years. Surgeons should stay abreast of the laws in their region governing the use of and indications for medicinal marijuana. Additional research is needed to provide further information on the widespread effects on the surgical patient and possible therapeutic modalities.

Funding sources

None.

Conflict of interest

No conflicts of interest for any author.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.10.053.

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