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CANNABINOIDS AS ANTIEMETICS: A SHORT REVIEW

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Abstract: Chemotherapy-Induced Nausea and Vomiting (CINV) remains one of the most frequent adverse effects of cancer chemotherapy, often leading to patient non-adherence to the prescribed chemotherapeutic regime, as well as several associated complications. Current antiemetic therapy has been reported to provide relief of CINV in 75-80% of patients, still leaving a margin for improvement. This makes the development and study of novel antiemetics, especially those providing relief of both early and late phases of CINV, a matter of prime importance. The purpose of this review is to illustrate the mechanism of action of cannabinoid substances and provide a general view of their current use as antiemetic drugs in clinical practice. Several research articles pertaining to the subject were compiled and studied. This review presents the information thereby obtained. It is concluded that cannabinoids possess value as antiemetic drugs, along with certain properties that set them apart from other classes of antiemetic substances.

Keywords: emesis, nausea, vomiting, chemotherapy, cancer

Cancer is a disease characterized by high indices of morbidity and mortality (14,1 million new cases were diagnosed in 2012, with 8,2 million cancer-related deaths occurring that same year) (1). On the basis of these statistics, any adverse effect of the prescribed pharmacologic regimen further aggravating the patient's condition, and/or causing patient non-adherence, is a serious concern for the modern clinician. Adverse effects induced by cancer chemotherapy, with Chemotherapy-Induced Nausea and Vomiting (CINV) among the most frequent, have been shown to be a fairly common cause of non-adherence in cancer patients (2, 3, 4). In addition, CINV itself may lead to several direct adverse effects, such as electrolyte disturbances, dehydration, metabolic alkalosis, (5) esophagitis and/or gastritis, gastroesophageal laceration (Mallory-Weiss syndrome) and associated hematemesis (6), as well as erosion of the tooth enamel.

Therapeutic regimen in CINV is mainly based on guidelines published by the European Society of Medical Oncology (ESMO) and Multinational Association of Supportive Care in Cancer (MASCC) (7). Generally they focused on a four-level classification of intravenous (i.v.) chemotherapy drugs producing recommendations on antiemetics: high (emetic risk > 90%), moderate (30–90%), low (10–30%), and minimal (< 10%) (8). Moreover, also new oral anticancer drugs have been introduced since the last MASCC/ESMO antiemetic guideline update (7). Briefly, excepting classical prevention model including three-drug management scheme (5HT3- antagonists like ondansetron, granisetron, dolasetron, tropisetron or palonosetron, dexamethasone and aprepitant as an NK1 antagonist), recent investigations revealed clinical acceptance for new NK1 antagonists: netupitant and rolapitant (7).

While current antiemetic therapy has been reported to provide relief of CINV in 75-80% of patients (9) that still leaves a high percentage of patients affected by CINV and the aforementioned consequences, including chemotherapy discontinuation.

Thus, the development and study of new antiemetic substances, especially those providing relief of both early and late phases of CINV, such as cannabinoids, is a matter of prime importance (10).

Emesis

The emetic reflex is a complex process, involving both Central Nervous System (CNS) and peripheral tissues, with several different neurotransmitters and related substances acting on a variety of different receptors. There are many factors leading to nausea and emesis to a degree that would require antiemetic therapy. However, CINV is emphasized

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in this article due to its prevalence in contemporary research, and the seriousness of the conditions it is associated with. In the context of CINV, the emetic reflex is divided into two phases: The early phase occurs within the first 24 h post-administration and is believed to be associated with 5-HT3 receptors and vagal afferents (11, and the delayed phase occurs between 3 and 7 days post-administration and is thought to occur due to activation of NK1 receptors located along the brainstem (9, 12).

Central emetic circuits

The Dorsal Vagal Complex (DVC) is the main brainstem structure involved in triggering the emetic reflex (9). The DVC consists of three nuclei: Area Postrema (AP), Dorsal Motor Nucleus of the Vagal Nerve (DMNX), and the Nucleus Tractus Solitarius (NTS), as well as other structures, such as the Central Pattern Generator Area (CPG).

Induction of CINV involves stimulation of all aforementioned areas. The fenestrated capillaries in the Chemoreceptor Trigger Zone (CTZ), found in the AP, allow several emetic compounds to cross the Blood-Brain Barrier (BBB), stimulating the aforementioned circuits, thus inducing emesis (13). The structures that form the DVC contain a variety of receptors, including dopaminergic – D2, D3, serotoninergic – 5-HT3, neurokinin 1 – NK1, and cannabinoid 1 – CB1. The CB1 receptors, in particular, are believed to play a key role in central emetic regulation (14), and it is through them that cannabinoids exert their antiemetic action (9, 15).

Peripheral emetic circuits

The peripheral structures linked to the emetic reflex are the afferent branches of the Vagal Nerve, as well as almost the entirety of the Enteric Nervous System (ENS) (16). The latter consists of numerous neuronal fibers forming the myenteric (Auerbach) plexus, and the submucosal (Meissner) plexus, as well as other minor plexi (17). All these structures are associated with the regulation of motility in the alimentary tract and are thought to be a separate part of the autonomic nervous system. This system's main transmitter is acetylcholine. A plethora of different receptors can be found in the peripheral emetic nerve tracts, including muscarinic – M, serotonergic – 5-HT (18), dopaminergic – D (19), GABA, opioid (20), as well as cannabinoid receptors – CB1 and CB2 (14).

Cannabinoids

Cannabis is an annual plant belonging to the family *Cannabaceae* and genus *Cannabis* which has been used as a psychoactive drug for centuries. *Cannabis* is a widely known plant, not only for its ritual and recreational use in several cultures throughout history, but also for its therapeutic use, with the first records dating back to 2737 BC in ancient China (Shen Nong) (21).

In European medicine, cannabinoids emerged as potential drugs in the 1840s, by the hand of William Brooke O'Shaughnessy, the Irish physician, toxicologist, and chemist (22, 23).

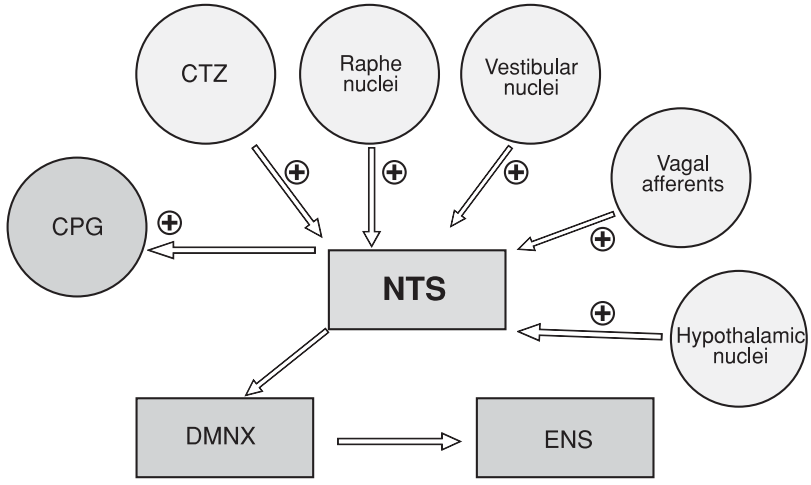

Figure 1. Structures of the dorsal vagal complex

CPG: Central Pattern Generator Area; CTZ: Chemoreceptor Trigger Zone; DMNX: Dorsal Motor Nucleus of the Vagal Nerve; NTS: Nucleus Tractus Solitarius; ENS: Enteric Nervous System

Nowadays, derivatives of *Cannabis* are known as cannabinoids, the most frequently used in contemporary practice being Δ-9-trans-Tetrahydrocannabinol (Δ-9THC), which is a psychoactive agent. Other natural cannabinoid products have been isolated and studied for biological activity, such as D8 -THC (also psychoactive), cannabinol, and cannabidiol (CBD) (both nonpsychoactive in common sense) (24). The chemical structure of these compounds is diverse. The term "cannabinoids" encompasses derivatives of dibenzopyran (classical cannabinoids), eicosanoids and indoles (25). These compounds are characterized by their analgesic, orexigenic, and antiemetic properties, and possess potential therapeutic use in conditions such as anorexia nervosa, glaucoma, epilepsy, and, most relevant to this article, emesis (26). In addition to the natural cannabinoids and derived analogs, the first of several endogenous ligands operating in the endocannabinoid system was isolated and characterized in the early 1990s (25). This so-called endocannabinoid was found to be the arachidonic acid derivative N-arachidonoyl ethanolamide (anandamide, AEA) and since its discovery several other endocannabinoids, found not only in mammals, have been reported and extensively studied for biological activity, including 2-arachidonoyl-glycerol [2-AG; (27)], 2-arachidonylglycerylether [noladin ether; (28)], and O-arachidonoyl ethanolamine [virodhamine; (29)].

Cannabinoids exert their effects by acting on cannabinoid receptors CB1 and CB2, located in the Central Nervous System (CNS), Enteric Nervous System (ENS), hematopoietic and inflammatory cells, as well as non-CB1/ non-CB2 receptors: GPR18, and GPR55 (24, 30, 31, 32, 33). The aforementioned receptors cooperate with a G-protein (GPCR) – in the case of cannabinoid receptors, a G-protein, which inhibits production of cyclic adenosine monophosphate (cAMP) (34). A decrease in cAMP concentration results in the activation of Ir- potassium channels, and inhibition of calcium membrane conductance. This process is essential for neural cell potential stabilization. Both CB1 and CB2 are metabotropic receptors built up of 7 transmembrane domains, an external N-terminus and an internal C-terminus. Cannabinoid receptor activation, especially that of CB1 receptors, mimics the effect of endocannabinoid ligands (e.g. 2-AG) on the neurotransmission systems, resulting in retrograde inhibition of signal transmission (retrograde antagonism), reduction of the amount of neurotransmitter released from the presynaptic membrane, and abolition of neuronal activation (35). It is through their agonistic action on CB1 receptors that cannabinoids exert their antiemetic properties. In contrast, CB2 receptors are attributed no direct relevance in the emetic process and are believed to play a role in immunomodulation (9, 15, 36).

CANNABINOIDS AS ANTIEMETICS

Antiemetic effects against experimentally-induced vomiting have been demonstrated using THC, its synthetic analogs and CBD (15, 37-39). A prime example of CBD's antiemetic activity is an experiment performed with shrews, which demonstrated that the compound is a potent suppressor of LiCl-induced vomiting (39). Cannabinoids exert their antiemetic actions at several different sites along the emetic sequence. Action upon presynaptic CB1 receptors leads to an inhibition in neurotransmitter release from the associated vagal afferent terminals, which in turn prevents afferent transmission of the emetic impulse. The effect is also exerted directly upon the terminals of inhibitory NTS interneurons, as well as NTS neurons with projections to both AP and DMNX and, finally, on receptors on AP neurons with projections to the DMNX and NTS (14). Molecular activity of antiemetic cannabinoids may be confirmed by a decreased expression of Fos-IR in the DVC following administration. This particle is a transcription factor, and its appearance is concomitant with forced neuronal activity (37). A particular quality of cannabinoids in their antiemetic action is the fact that, as previously described, they exert their antiemetic properties by acting as CB1 receptor agonists (9, 15). Moreover, from the results of preclinical studies, it is known that the antiemetic effects of CBD may be mediated by indirect activation of somatodendritic 5-HT(1A) receptors in the dorsal raphe nucleus. Activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions. It is thanks to these agonistic actions upon different receptors that cannabinoids may be clinically effective in treating nausea and vomiting produced by chemotherapy and other therapeutic treatments (40). This is in contrast to most other antiemetics, which exert their effects by antagonizing the receptors of emetogenic substances, such as dopamine, serotonin, acetylcholine and substance P. One of the chief reasons behind the recent interest in the antiemetic properties of cannabinoids stems from the fact that they act on both acute and delayed phases of emesis (9, 37). It is worth noting that no single currently available antiemetic, (including cannabinoid substances) provides complete relief for both phases.

Another aspect conferring cannabinoids a high potential value as antiemetics is their broad-spectrum of use against different emetogens beyond the

aforementioned CINV. Some examples being Radiation-Induced Nausea and Vomiting (RINV) (41), opioids (38, 42), arachidonic acid (43) and even some bacterial toxins (44), as well as motion (45). Most notable is their effect on both CINV and RINV, two commonly occurring adverse effects of oncologic treatment due to the frequent use of combined chemo- and radio-therapy.

Clinical use of cannabinoids as antiemetics

One of the first clinical reports concerning the use of cannabinoids in controlled clinical situations was reported by Sallen et al. (46). Since that time, only a few clinical reports concerning the use of cannabinoids as antiemetics can be found. One such report is the review by Tramer et. al (47), a systematic review of 30 randomized comparisons of cannabis with placebo or antiemetics. It was understood that in all 1366 patients involved in the review, the cannabinoids were found to be significantly more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. Ben Amar summarized 15 controlled studies comparing nabilone (a synthetic analog of THC) to placebo or available antiemetic drugs and concluded that in 600 patients with a variety of malignant diagnoses, nabilone was found to be superior to prochlorperazine, domperidone, and alizapride (48). Relatively recently, a small pilot, randomized, double-blind, placebo-controlled phase II trial was conducted to investigate the whole-plant cannabis-based medicine, nabiximols (THC : CBD, 1 : 1), added to standard antiemetics in the treatment of CINV (49). In this study, 7 patients were randomized to receive the drug, and 9 added placebo to their standard of care antiemetic regimen. The results showed that 5 of the 7 nabiximols recipients experienced a complete response without serious adverse effects. To our knowledge, there is no further available clinical trial data concerning antiemetic use of the drug.

Cannabinoids, albeit rarely as a first-line agent, are often prescribed as antiemetic medication. Two of the main properties setting cannabinoids apart from other antiemetics are, as this article has illustrated, their ability to act on several locations along the emetic circuits, as well as their action on both early and delayed emetic phases (37). Other important aspects of the clinical use of these substances are their orexigenic and analgesic properties, which make them relevant in conditions were nausea and emesis coexist with either a loss of appetite or debilitating condition (such as cancer or AIDS) and/or mild pain (48). Additionally, cannabinoids show potential as backup drugs in situations where other antiemetic treatment options have proved inappropriate due to qualities inherent specifically to those substances. This is due to the action of cannabinoid substances on their very own cannabinoid receptors (9, 15), granting them a mechanism of action different from those of more typical antiemetics.

Cannabinoid adverse effects

A broad spectrum of adverse effects are associated with the clinical use of cannabinoids, the most common being dizziness, xerostomia, fatigue, somnolence, drowsiness, behavioral and/or mood changes, feelings of intoxication, confusion, both euphoria and dysphoria, anxiety, hypothermia, locomotor suppression, disorientation, appetite stimulation (which can often be beneficial, for instance in debilitating diseases such as cancer and AIDS) (48), generalized weakness, psychosis, hallucinations and suicidal ideation (48, 50, 51, 52). Several of the aforementioned adverse effects have been reported to be dose-dependent, and directly related to the THC content of the preparation (50, 53). It is worth noting that, when used recreationally, with no controlled dose, some cannabinoid preparations have been reported to cause nausea. Additionally, cannabinoids act as inhibitors of many of the enzymes that compose the cytochrome – 450 system, which results in drug interactions with other substances.

No deaths directly caused by a cannabinoid overdose have been reported, not even in the context of non-clinical, recreational use. However, fatalities, often due to trauma, have been reported to occur secondary to the impaired judgment associated with cannabinoid use (50). It is also worth noting that cannabinoids that are smoked should be expected to exhibit adverse effects associated with this route of administration (50).

Finally, there have been reports of cognitive impairment associated with long-term cannabinoid use, especially in patients with pre-existing conditions also causing a cognitive dysfunction (54, 55).

Cannabinoid hyperemesis syndrome

Cannabinoid Hyperemesis Syndrome (CHS) is a paradoxical and only partly understood adverse effect of chronic cannabinoid use first described in 2004 (56). The exact pathogenesis of CHS remains unknown, although it has been suggested the syndrome may be caused by cumulative Δ9-THC CNS toxicity over a long period of time (57). Although the amount of research data collected regarding CHS continues to steadily increase, a retrospective study performed in 2012 suggests the syndrome is

often under-recognized and, consequently, underdiagnosed in clinical practice (58, 59).

CHS is characterized by recurrent episodes of severe nausea and vomiting, diffuse, colicky abdominal pain, and compulsive hot-water bathing (which has been reported to transiently alleviate the symptoms) (59). Electrolyte imbalances, weight loss, and all other previously mentioned consequences of chronic emesis may occur secondary to CHS if the condition persists. There seem to be no triggers or exacerbating factors and the condition responds poorly to antiemetic treatment. Lorazepam and Haloperidol are thus far the only medications reported to provide symptom relief (59, 60). CHS does, however, subside within days once cannabinoid use ceases (61, 62).

Adverse effect control

While some of the previously illustrated adverse effects could prove limiting in certain patients, it is worth noting that the clinical use of cannabinoids is a popular field in contemporary research, with still a lot to be learnt. There is certainly still potential for improvement, with the reduction of adverse effects not being an exception. For instance, the use of selective endocannabinoid reuptake inhibitors, such as OMDM-1 and UCM-707 has been proposed as a method to reduce the adverse effects associated with THC's psychoactive properties (9). However, a side effect that, due to its paradoxical nature would likely require discontinuation of cannabinoid use, and treatment with a different antiemetic medication, is the previously illustrated Cannabinoid Hyperemesis Syndrome (56). Fortunately, CHS has only been known to appear after long-term cannabinoid use, and may thus often not become an issue during a course of antiemetic treatment. In addition, as previously mentioned, it is easily reverted by discontinuation of cannabinoid use and replacement with a different antiemetic medication, without any further consequences (61, 62).

CONCLUSION

Cannabinoids possess documented antiemetic activity, and have proven useful in the treatment of nausea and vomiting, including CINV. A series of additional effects make cannabinoids particularly useful when nausea and vomiting present with other comorbid conditions.

Conflict of interest

Authors declare no conflict of interest.

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