Established and potential therapeutic applications of cannabinoids in oncology

Abstract  Cannabis occurs naturally in the dried flowering or fruiting tops of the Cannabis sativa plant. Cannabis is most often consumed by smoking marijuana. Cannabinoids are the active compounds extracted from cannabis. Recently, there has been renewed interest in cannabinoids for medicinal purposes. The two proven indications for the use of the synthetic cannabinoid (dronabinol) are chemotherapy-induced nausea and vomiting and AIDS-related anorexia. Other possible effects that may prove beneficial in the oncology population include analgesia, antitumor effect, mood elevation, muscle relaxation, and relief of insomnia. Two types of cannabinoid receptors, CB1 and CB2, have been detected. CB1 receptors are expressed mainly in the central and peripheral nervous system. CB2 receptors are found in certain nonneuronal tissues, particularly in the immune cells. Recent discovery of both the cannabinoid receptors and endocannabinoids has opened a new era in research on the pharmaceutical applications of cannabinoids. The use of cannabinoids should be continued in the areas indicated, and further studies are needed to evaluate other potential uses in clinical oncology.

Keywords  Cannabinoids · Delta-9-tetrahydrocannabinol · Anorexia · Nausea and vomiting

Introduction

Cannabis preparations have been used for their psychotomimetic effects for over 4000 years. Their medicinal properties have been suggested since antiquity [1]. Marijuana was listed in the US Pharmacopoeia until 1944 [2], when it was removed owing to growing political pressure to ban its social use in the United States. It has not been reinstated, but in 1986 its active ingredient, delta-9-tetrahydrocannabinol (THC) was granted FDA approval. A semisynthetic THC-like material, synhexyl, was tested as a therapeutic agent during the late 1940s and early 1950s. Initial trials reported its efficacy as an antidepressant and as a treatment for the symptoms of alcohol or opioid withdrawal, but subsequent clinical evaluations were negative [3]. There are now three other synthetic cannabinoids that have been evaluated in clinical trials: dronabinol, nabilone and levonantradol. Dronabinol (Marinol, Unimed, Marietta, Ga., USA) is the synthetic form of THC that is commercially available today. Currently, there are only two approved indications: cytotoxic chemotherapy-induced nausea and vomiting, and AIDS-associated anorexia and wasting.

Recently, there has been renewed interest in marijuana for medicinal purposes. This has been prompted most recently in the US by legislation in California and Arizona, and in the UK by a vote of the British Medical Association membership (their governing body did not agree) to expand its use. Unfortunately, any medicinal value of cannabis is tempered by the vehicle (marijuana) by which it is most commonly ingested. Except for N-nitrosodimethylethanolamine, marijuana has all the same chemical carcinogens as are found in tobacco. There are multiple chemicals in a marijuana cigarette, making it potentially harmful in long-term use and difficult to investigate in clinical trials. There has been some resolution of this
Table 1 Pharmacokinetics (NA not applicable)

<table>
<thead>
<tr>
<th>Route</th>
<th>Peak concentration</th>
<th>Half-life</th>
<th>Peak effects</th>
<th>Duration of action</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation [37]</td>
<td>Within minutes</td>
<td>28–57 h</td>
<td>15–90 min</td>
<td>&lt;2–4 h</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Decreases to 10% of the peak level in 1–2 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous [38]</td>
<td>Within minutes</td>
<td>NA</td>
<td>30 min</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Oral [38, 39]</td>
<td>2–4 h</td>
<td>36 h</td>
<td>30–180 min</td>
<td>4–6 h for psychoactive</td>
<td>10–20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h for appetite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Physiological effects

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypotension</td>
</tr>
<tr>
<td></td>
<td>Decreased cardiac function: EF, LVED volume, stroke index</td>
</tr>
<tr>
<td>CNS</td>
<td>Cognitive deficits: perception, memory, reaction time, coordination</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Bronchodilatation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased motility, delayed gastric emptying</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Decreased muscle strength</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Chronic use: decreased testosterone and sperm count</td>
</tr>
<tr>
<td>Other</td>
<td>Conjunctival reddening, intraocular pressure decrease</td>
</tr>
</tbody>
</table>

Routes of administration

The route of administration (Table 1) affects the time course and intensity of cannabinoid effects. It is important, when reviewing the literature on marijuana/cannabinoids, to know the route of administration used in the study. Inhalation may mean ingestion of a purified, often single, cannabinoid via a mechanical device. The known potential long-term health hazards of this approach are considerably less than those of smoking marijuana. It is difficult to quantitate these hazards in the cancer patient, as their smoking is not the same in quantity or duration as in most tobacco smokers, for whom the health consequences are obvious. In addition, the results obtained using a single agent (e.g., THC rather than marijuana) and a specific dose are much more reliable. Like tobacco, marijuana cigarettes contain carcinogenic material [4]. When cannabis is smoked, a variable fraction of THC is lost into the air or from the respiratory dead space and a small amount by pyrolysis. It is also mixed with CBD and CBN, possibly influencing its pharmacokinetics. Many uncontrollable factors (questionable content, amount and smoking technique) in pharmacokinetic analysis (and presumably in clinical action) may be introduced. THC plasma levels after smoked marijuana depend on dose, route of administration, experience of the user, method of smoking (overall time duration of ingestion, inhalation duration, volume inhaled, breath-holding after inhalation) and the individual preference/tolerance for psychoactive effect. If marijuana is of low potency, effects may be subtle and brief.

The bioavailability of THC ingested smoking marijuana is about 18%; frequent smokers obtain 23%, and infrequent users only 10% [12]. There have been unsuccessful attempts to correlate the pharmacologic effects of THC with plasma levels. There is a 15-min lag between achievement of peak plasma levels and euphoria with inhalation and a lag of 1 h for oral administration (2 h after ingestion). The only commercially available oral cannabinoid in the US is the synthetic THC, dronabinol. After oral administration 90–95% is absorbed. Only 10–20% reaches the circulation owing to hepatic first-pass metabolism. The effects of intravenous (i.v.) administration of THC are similar to those of smoking [13]. In experienced marijuana users, THC suppositories were as effective as smoked marijuana in increasing caloric intake. The plasma levels increased and decreased more quickly with the inhaled drug, but suppositories produced a more sustained level.

Acute effects

One of the first effects of marijuana is a constant increase in pulse rate. Blood pressure tends to remain stable or fall slightly. Conjunctival reddening and decreasing muscle strength are observed [14]. There is no effect on pupil size, respiratory rate or deep tendon reflexes (Table 2).

Psychotomimetic effects are biphasic, with an initial euphoria followed by relaxation and drowsiness, and correspond more closely to those of the THC metabolite 11-hydroxy-THC than to those of the parent compound (Tables 3, 4). These psychotomimetic effects are extremely variable and pronounced in those smoking marijuana, but not necessarily in the controlled environment of medical prescribing. In the studies of THC in cancer patients, the drug is well tolerated. The physiological effects corre-
problem with the development of dronabinol. Other possible uses that may prove beneficial in the oncology population include analgesia, muscle relaxation, mood elevation, and relief of insomnia. We may be able to expand the use of dronabinol safety through well-designed clinical trials and properly controlled distribution.

Chemistry

Cannabis is the collective term for psychoactive compounds occurring naturally in the Cannabis sativa plant. Specifically, its pharmacologic and psychoactive compounds are C21 cannabinoids; these are found in all parts of the plant but the most potent resinous exudate comes from the flowering tops. The potency of the clinical effects is determined by the type of seed and the part of the plant being used and not by the climate or soil, as had once been assumed [4]. The most common method of cannabis ingestion in the US is by smoking marijuana. It is derived from any part of the dried plant and generally rolled into a cigarette-type vehicle. More potent preparations, such as hashish (the Middle East, North Africa), charas (India) and ganga (Jamaica), are derived from the resin taken from flowering tops of the plant and are eaten, drunk or smoked. The THC content is 5% of dry weight in the case of marijuana, as against up to 10% of hashish and 20% of hashish oil [5].

Of the more than 400 chemicals in marijuana, at least 60 are cannabinoids. The principal active constituent, THC (Fig. 1), was first isolated in pure form from hashish in 1964. It was obtained by extraction with petroleum ether and then subjected to repeated chromatography [5]. The process of identification was complicated by the nonalkaloid nature of the drug, the large number of unstable compounds, and the difficulty in crystallizing them in the underivatized state. Other important cannabinoids include delta-8-THC (8-THC), cannabiol (CBN) and cannabidiol (CBD). Together, their concentration in marijuana-type cannabis preparations is 1–2%. THC has profound psychotomimetic (cannabinimetic) effects, CBN has about 1/10th its psychoactive potency, and CBD has none [4]. 8-THC has cannabimimetic properties similar to those of THC, but occurs in such small amounts that its effects are considered insignificant. The cannabinoids are highly lipid soluble, with a pKa value of 10.6 [4]. With the multiple substances in marijuana, particularly the cannabinoids, it is possible that these substances work synergistically, additively, or even antagonistically when ingested together by smoking. This has significant implications for the clinical usefulness of marijuana or its individual compounds.

Pharmacology

In animal studies, THC and nabilone share some properties with morphine in a chronic pain model. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors [4]. Cannabinoid receptors (CB1 and CB2) were discovered in the late 1980s and found to mediate the effects of cannabinoids on the nervous system. CB1 receptors are expressed mainly in the central and peripheral nervous system. CB2 receptors are found in certain nonneuronal tissues, particularly in the immune cells. This led to the design of synthetic cannabinoid agonists and antagonists with high therapeutic potential. The recent discovery of the endocannabinoids, i.e. endogenous metabolites capable of activating cannabinoid receptors, and the understanding of the molecular mechanisms leading to their biosynthesis and inactivation, opened up a new era in research on the pharmaceutical applications of cannabinoids, e.g. in the management of pain and in the suppression of muscle spasticity/spasm associated with multiple sclerosis or spinal cord injury [5, 6, 7, 8]. Recent results with cannabinoids and their receptor ligands have shown they bind the NMDA receptor, suggesting they may be useful in neuropathic pain [9]. There have been reports that the cannabinoids have some utility in retarding the growth of certain tumors. In mice, THC, 8-THC, and CBN, but not CBD, retarded implanted tumor growth and extended survival time in mice. These responses were dose related and were much higher than those necessary to produce central nervous system effects.

Most studies show that tolerance (the requirement of increasing doses to maintain the same clinical effect) develops to the psychotomimetic effects of marijuana and to the individual cannabinoids. Significant, rapidly developing tolerance has been observed in most animal and human experiments [10, 11]. This is both a pharmacodynamic and pharmacokinetic tolerance. Unlike that for opioids, there is a long duration of tolerance after cessation of the drug. Nonspecific cross-tolerance among various CNS depressants and cannabinoids has been reported. Cross-tolerance between ethyl alcohol and THC has also been demonstrated in laboratory rats.
Table 3  Psychological effects of THC in advanced cancer. (Adapted from [40])

<table>
<thead>
<tr>
<th>THC effect</th>
<th>Testing result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Decreased incidence, no decrease in severity</td>
</tr>
<tr>
<td>CNS function</td>
<td>No change</td>
</tr>
<tr>
<td>Concrete vs</td>
<td>No change</td>
</tr>
<tr>
<td>abstract thinking</td>
<td></td>
</tr>
<tr>
<td>Impulsivity</td>
<td>No change</td>
</tr>
<tr>
<td>Realism</td>
<td>Moved toward self-reliance</td>
</tr>
<tr>
<td>Apprehension</td>
<td>Trend toward reduction</td>
</tr>
<tr>
<td>Tension</td>
<td>More tranquil, relaxed</td>
</tr>
</tbody>
</table>

Table 4  General psychological effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>Higher doses:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation</td>
<td>Anxiety</td>
<td>Delusions</td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Improved sense of well-being</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered time sense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depersonalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulting concentrating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dream-like states</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

late with its plasma concentration and the onset and duration of psychotomimetic effects of the drug [4].

Chronic effects

In a study in Jamaica, where cannabis is legal and widely used, 30 ganja smokers were compared with 30 non-smokers. No significant physical abnormalities between the two groups were detected [15]. In another study from Costa Rica, where cannabis use is prevalent, no significant differences in workplace productivity were found between 74 users and 149 nonusing controls [16]. The mean duration of use was 10 years, with a frequency of three or more times a week. No differences were found between the groups in age, height, weight, blood pressure, heart rate, and an extensive battery of hematologic and biochemical blood tests. In a study from Greece, 47 chronic hashish users were compared with a nonusing, matched group of 40 controls [17]. The mean time of use was 23 years of smoking 2–6 g of hashish 2–3 times per day. The following tests/parameters revealed no difference between the study group and controls: bronchitis, emphysema, tooth decay, blood pressure, resting heart rate, central/peripheral nervous system abnormality, electroencephalogram, and third ventricle size. There were differences in the psychiatric testing, with the user group having a 38% incidence of psychopathology and the controls 17%. In most cases the psychopathology took the form of personality disorders; the other diagnoses were not statistically different between groups. The psychological assessment was also different. Controls scored better in several subtests, but there were no differences in total I.Q. measurement between the two groups.

These epidemiological studies are difficult to design, making their interpretation difficult. However, if they fail to show harm from long-term cannabis use, it may be difficult to contradict this in experimental studies. This may be a moot point in the cancer patient population, in whom it would be used medicinally in a controlled amount and over a limited duration of time.

Clinical use

Antiemetic

The synthetic homologue of THC, nabilone, was developed in 1972 and tested for antiemetic activity. Two studies have documented its antiemetic efficacy with cytotoxic chemotherapy, but significant psychotomimetic side-effects limit its usefulness [18]. Levonrantradol, another synthetic THC homologue, has antiemetic effects in open studies but the psychotomimetic side effects and hypotension limited its use [19]. Blockade of cannabinoid (CB1) receptors induces vomiting, suggesting a role for endogenous cannabinoids in emetic circuits. This also suggests the antiemetic activity of delta-9-THC is due to stimulation of the CB1 receptor [7].

To date, the largest body of clinical research of THC in cancer patients has been for chemotherapy-induced nausea and vomiting. The antiemetic effect of cannabis was suggested in 1972 [20]. Studies have documented the superior efficacy of THC over placebo and prochlorperazine [21, 22]. All used considerably higher doses than the subsequent appetite studies and were in generally younger populations. THC is effective against mild and moderately emetogenic chemotherapy, but not against high-dose cisplatin chemotherapy [23]. THC is superior to low doses of metoclopramide in patients receiving moderately emetogenic chemotherapy, but inferior to high-dose metoclopramide in cisplatin-based chemotherapy [23, 24]. Since the physiological and neuro-psychological side effects produced by higher doses are often disturbing to elderly people, THC is probably more useful as an antiemetic in younger patients. The toxicity of cannabinoids seems to be reduced and the effect to be increased by combination with prochlorperazine [25]. Currently, dronabinol 2.5–5mg orally is the recommended dose for chemotherapy-induced nausea and vomiting. With the newer antiemetics available, it remains a fourth-line agent for this indication.

Appetite stimulation

There is considerable anecdotal information about the effects of marijuana on food intake. Three studies
Table 5 Appetite studies with dronabinol

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Age</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[26]</td>
<td>Advanced cancer</td>
<td>61 years</td>
<td>2.5 mg t.i.d.</td>
<td>13/18 had improved appetite, Dose timing important</td>
</tr>
<tr>
<td>[27]</td>
<td>AIDS</td>
<td>39 years</td>
<td>2.5 mg b.i.d.</td>
<td>37% increase appetite for the population (N=42)</td>
</tr>
<tr>
<td>[40]</td>
<td>Cancer</td>
<td>Not reported</td>
<td>0.1–0.2 mg/kg</td>
<td>Group analysis—gained weight on THC, t.i.d.—q.i.d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lost weight on placebo</td>
</tr>
</tbody>
</table>

(Table 5) have evaluated the appetite-stimulating effects of oral THC in advanced cancer-associated anorexia [3, 23, 24, 25, 26, 27, 28]. In nine hospitalized patients (mean age 54 years), three doses were evaluated for 1 week in a double-blind crossover study to determine appetite, weight gain, and toxicity. The lowest dose, 0.1–0.12 mg/kg four times daily, was the only one tolerated without psychotomimetic dose-limiting effects. There was significant weight gain with THC and continued loss with placebo [3]. In another open-label study [26], 13 of 18 evaluable patients (mean age 64 years) had improved appetite with dronabinol, 2.5 mg p.o. given three times daily 1 h after meals (those over 60 years were started at twice daily dosing, which was increased after 2 days if the drug was well tolerated). Four developed psychotomimetic side effects. Appetite stimulation was not dependent upon the development of euphoria associated with the drug, as noted in some anxiometric studies. The low dose and timing were thought to be important in preventing the significant side effects seen in the other studies.

The appetite-stimulating properties have also been observed in the AIDS population in a double-blind, randomized, placebo-controlled crossover trial with two 5-week treatment periods [27]. The patients had a mean age of 37 years, and more than 50% had previous experience of smoking marijuana. With 2.5 mg once daily (10% of the study population) or twice daily (90% of the population) they reported an appetite increase over baseline for 12 months in the 24% of patients who were evaluable. Despite low dose and young age, 38% experienced typical psychotomimetic side effects, and half withdrew from the study because of side effects or declining performance status. Although there was no report of the effect of prior experience on response, we might expect that those more comfortable with the psychotomimetic effects would be more inclined to continue treatment. The long-term use of dronabinol in both these populations seems well tolerated [2, 27].

Mood effects

In an antidepressant/appetite study in advanced cancer, a median dose of THC 15 mg/day had a positive effect on several psychological parameters and no documented negative effects except in one patient who was "concerned over loss of sanity" (Table 3) [3]. In another study, 12 radiation therapy patients were given THC 10 mg every morning to enhance mood. The results revealed increased fatigue and lack of mood elevation, but patients reported subjective benefit in mood [30].

Miscellaneous

Recent evidence clearly demonstrates a therapeutic effect of THC on pain, muscle spasms, and tremor in multiple sclerosis [31]. The anticonvulsant effect of cannabidiol is sufficiently promising to warrant further properly designed clinical trials. Cannabinoids may reduce anxiety and improve sleep. Anecdotal evidence of cannabis use includes case reports or series in migraine, Tourette’s syndrome, glaucoma (reducing intraocular pressure), and bronchial asthma. Currently, a synthetic cannabinoid HU211 is undergoing trials as a protective agent after brain trauma [31, 32, 33].

Conclusions

Cannabinoids have many potential therapeutic effects in chemotherapy-induced nausea and vomiting, anorexia, anti-tumor, pain, insomnia, and muscle spasm. These benefits focus the attention to the future use of cannabinoids in clinical oncology [26]. Well-designed clinical trials should be conducted in the latter setting. The discovery of both CB1 and CB2 cannabinoid receptors and endogenous cannabinoids has directed research attention in understanding the physiology, pharmacology, and molecular basis of cannabinoids. This information will help in the development of new synthetic cannabinoid agonists, finding possible therapeutic applications, and separating the wanted and unwanted effects of cannabinoids [5, 6, 35].

We have a good idea of the acute effects of cannabinoids, although these are modified by the dose, route of administration and, possibly, by past experiences. The

Analgesia

In a double-blind crossover study comparing single oral doses of 10 mg and 20 mg of THC to codeine (60 mg and 120 mg) in chronic cancer pain, the 20-mg THC dose was comparable to both doses of codeine for analgesic efficacy [29].
effects of chronic use have been defined primarily in field studies that fail to clearly reveal any significant health consequences of chronic use. Although the short-term use of dronabinol has been seen to be safe in many studies, this observation cannot be extrapolated to the use of marijuana, which has not been subjected to clinical trials, contains additional compounds not found in dronabinol, and has been used primarily in a young, healthy population.

The major disadvantage is that psychotomimetic effects are produced by the doses given. Studies suggest that tolerance develops rapidly and is sustained. Since these studies are for the usual psychotomimetic effects, we do not know whether the same occurs for the desirable antiemetic and appetite-stimulating effects. The possibility that there may be tolerance for the unwanted (in the cancer patient) effects with continued efficacy in terms of appetite stimulation and control of nausea and vomiting deserves further investigation. Further studies should evaluate dose ranges and drug combinations to lower the side effect profile and increase the efficacy. A particularly interesting area would be the combined use of NSAIDs and THC for control of mild to moderate cancer pain. The current data suggest that once-daily dosing may be acceptable for some indications and the development of a sustained-release preparation may be feasible and useful. While THC is an effective antiemetic, its use for chemotherapy-induced nausea and vomiting will probably remain limited. However, its use as an appetite stimulant seems appropriate but should be expanded and further investigated.

Inhalation of THC or another cannabinoid, possibly by nebulizer, is potentially useful in nausea, where oral intake can exacerbate the symptoms, in polypharmacy, where patients are already taking many pills to control multiple symptoms. If further studies support the analgesic benefit of THC, inhalation may have particular potential in neuropathic pain and for controlling incident pain, where infrequent use with rapid onset is necessary. Inhalation also offers enhanced patient-controlled use by the degree and timing of inhalation and warrants further investigation. THC may also be useful to modify the affective response to pain. Lastly, there is the potential subjective benefit of an improved sense of well-being through the use of a safe drug prescribed in a controlled and monitored setting.

The question of the medicinal value of marijuana compounds should be answered, but not solely in the political arena [35]. We need systematic research. The decision to use cannabinoid for symptom relief in cancer should be based on well-designed clinical trials conducted in the oncology population. It seems prudent to focus on a high-quality, legally available drug such as dronabinol, rather than marijuana, as well-controlled studies would be easier to design and yield results of greater integrity.

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