Assessment of Delta-9-Tetrahydrocannabinol (THC) in Saliva and Blood After Oral Administration of Medical Cannabis With Respect to its Effect on Driving Abilities

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Received March 24, 2022
Accepted August 23, 2022
Epub Ahead of Print September 19, 2022

Summary

Medical cannabis has recently been legalized in many countries, and it is currently prescribed with increasing frequency, particularly for treatment of chronic pain resistant to conventional therapy. The psychoactive substance delta-9-tetrahydro-cannabinol (THC) contained in cannabis may affect driving abilities. Therefore, the aims of this study (open-label, monocentric, nonrandomized) were to evaluate blood and saliva concentrations of THC after oral administration of medical cannabis and to assess the time needed for THC levels to decline below a value ensuring legal driving. The study involved 20 patients with documented chronic pain using long-term medical cannabis therapy. They were divided into two groups and treated with two different doses of cannabis in the form of gelatin capsules (62.5 mg or 125 mg). In all patients, the amount of THC was assessed in saliva and in blood at pre-defined time intervals before and after administration. THC levels in saliva were detected at zero in all subjects following administration of both doses at all-time intervals after administration. Assessment of THC levels in blood, however, showed positive findings in one subject 9 h after administration of the lower dose and in one patient who had been given a higher dose 7 h after administration. Our finding suggested that for an unaffected ability to drive, at least 9-10 h should elapse from the last cannabis use.

Key words

Delta-9-tetrahydrocannabinol • Cannabis • Driving abilities • Chronic pain treatment

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Introduction

Medical cannabis (also called medical marijuana) and its possible therapeutic uses have received rapidly increased attention during past few years. It has recently

been legalized in many countries around the world (e.g. within Europe: Czech Republic, Denmark, Germany, Italy, United Kingdom) [1]. The main indications involve chronic persistent pain (associated with cancer, neuropathic pain, or pain related to degenerative disease of the musculoskeletal system) and, furthermore, spasticity and pain in multiple sclerosis. Moreover, it can be very beneficial in the treatment of many other medical conditions (e.g. a tremor caused by Parkinson's disease, nausea and vomiting particularly following cancer treatment, stimulation of appetite in cancer and HIV patients, Tourette syndrome, and superficial treatment of dermatosis and mucosal lesions) [2].

Medical cannabis usually refers to the dried flowers of female *Cannabis sativa* or *Cannabis indica* plants. These annual dioecious plants contain over 1400 natural compounds, of which at least 144 are plant-specific and termed cannabinoids [3,4]. Although cannabinoids in general have drawn attention for many years, the last four decades have been crucial for research on them, bringing completely new and scientifically relevant insights into their mechanisms of action.

It has been shown that cannabinoids act primarily on specific cannabinoid receptors CB_1 and CB_2; nevertheless, they may also affect many other receptor structures including GPR55, GPR18, GPR119 receptors, TRPV1, TRPV2, TRPA1, TRPM8 receptors, and nuclear receptors (PPARs) [5-8].

The best described cannabinoid receptors are CB_1 and CB_2. CB_1 receptors are found especially in the CNS in areas of the brain responsible for movement, pain modulation, and memory [9,10]. They are also present (though in smaller amounts) in some peripheral tissues such as immune cells, reproductive tissues, pituitary gland, gastrointestinal tissues, and heart. In contrast, CB_2 receptors are expressed particularly in the peripheral tissues (immune cells, tonsils and spleen) [11,12], but they have also been found to a limited extent in the CNS [13]. Thus, as is apparent from cannabinoid receptors' ubiquitous distribution, these substances may play many important roles throughout the body.

The most studied cannabinoids from cannabis include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a partial agonist of cannabinoid CB_1 and CB_2 receptors, whereas CBD is referred to as a negative allosteric modulator of CB_1 receptors (thus decreasing the effects of their agonists including THC), and moreover it acts as an antagonist/inverse agonist of CB_2 receptors [14,15].

Significant psychoactive effects having an impact on cognitive abilities and mental functions including attention, psychomotor performance, and reaction time (and therefore on driving abilities) – are attributed only to THC, and its psychotropic effects in general are mediated primarily by the activation of CB_1 receptors [16,17].

Varieties of cannabis differ greatly in their THC contents ranging from industrial hemp with less than 0.3 % to strains producing higher amounts of THC that have been recently cultivated, and which may contain up to 25 % of THC in the dried inflorescence [18].

The absorption of THC after cannabis oral administration depends to a large extent on drug dosage form, excipient, and whether it was taken with or without food. Furthermore, it is affected by degradation in the stomach and a significant first-pass effect in the liver. Bioavailability of THC following oral administration is variable, and in general low (4-20 %) [19].

Additionally, physiological factors, such as intestinal motility (intestinal atony, constipation, diarrhea), pathophysiology (liver functions), and co-medication play a significant role in the rate and extent of the bioavailability and also the clearance of cannabinoids [2,19,20]. For instance, antispasmodics, parasympatholytics, prokinetic agents, antiemetics (metoclopramide, itopride), setrons, antidiarheals (loperamide, difenoxylate), and also psychotropics with antimuscarinic properties may significantly change pharmacokinetic parameters. Depending on the administered dose and drug dosage form, the time necessary for reaching maximum concentration ranges between 0.6 and 2.6 h [21-23].

THC is very lipophilic substance (volume of distribution 3.4 l/kg). It crosses the placenta and binds to plasma proteins (up to 99 %) [19,24]. It can accumulate in adipose tissues with long-term use. Following release and redistribution, particularly in chronic users, this can (depending on the dose) lead to the persistence of cannabinoid activity for days or even weeks after administration [25,26].

The metabolism of THC takes place mainly in the liver, *via* cytochrome P450 (CYP 450) isozymes CYP2C9, CYP2C19 and CYP3A4. The principal metabolites of THC are 11-hydroxy-THC (11-OH-THC) and 11-carboxy-THC (11-COOH-THC). They undergo glucuronidation and are excreted in the faeces and urine. Metabolism can be also found in the small intestine and brain [26].

After oral administration, a lower absorption rate compared to inhalation or oromucosal administration is

observed, with THC T_{max} of approx. 0.6 to 2.6 h, depending on the dose and drug dosage form [27-29].

The volume of distribution is reported to increase with chronic administration [19]. The elimination of cannabinoids after conventional oral administration is best represented by the two-compartment elimination model. The distribution half-life ($T_{1/2\alpha}$) is about four hours and the terminal elimination half-life ($T_{1/2\beta}$) is 24 to 38 h [30]. The terminal elimination half-life may be prolonged in chronic users [19]. Interestingly, serum levels of ALT seem to be a useful predictive marker of THC clearance and co-variate in pharmacokinetic models since a close correlation between serum ALT levels and elimination rate constant was found [31]. Similar pharmacokinetic profile as THC show also major metabolites 9-hydroxy- and 11-hydroxy-THC [19,28].

The use of medical cannabis has been legal in the Czech Republic since 2013; however significant utilization of drug dosage forms containing raw hemp only followed the publication of the legislative norm valid since 2015 (Decree No. 236/2015 Coll.). In this country the most frequently used types of cannabis to be commonly prescribed for the treatment of chronic pain usually contain 18-23 % THC, and their routes of administration particularly involve vaporization and oral intake in the form of hard capsules. The use of capsules containing medical cannabis was initiated for the first time in the pharmacy of St. Anne's Faculty Hospital (Brno) some years ago [2] and the capsules has shown to be very suitable and accurate drug dosage form for these purposes.

Patients are given cannabis especially for the treatment of pain of various origin that has been shown to be resistant to conventional treatment methods.

It is not surprising that increasing numbers of patients prescribed medical hemp have raised the crucial questions of how long their driving abilities are affected and how long THC (or its metabolites) can be detected in the blood.

Relationship between levels of THC (or of its metabolite 11-hydroxy-THC) and effects on driving abilities is not completely clear yet, but it appears that the level which significantly impairs psychomotor performance and ability to drive is about 4 ng/ml. This level affects driving ability similarly to 0.4 ‰ of alcohol [32]. For forensic purposes, the THC level in the blood must not be higher than 2 ng/ml when driving in the Czech Republic. We therefore decided to use saliva and blood THC levels to estimate safe/legal driving instead of driving abilities testing.

It is well known from studies dealing with the use of cannabis for recreational purposes that THC seriously impairs psychomotor performance [33]. However, no published precise pharmacokinetic studies, using non-extracted medical cannabis in capsules and showing the effect of their repeated administration on the ability to drive, have, to our knowledge, been published to date.

Therefore, the aims of this study were twofold: 1) evaluation of blood and saliva concentrations of THC at predefined time intervals after medical cannabis oral administration; and 2) the assessment of the time needed for THC levels to decline below 2 ng/ml (i.e. the level ensuring legal driving). The presented study was carried out within the Clinical Pharmacology Unit (International Clinical Research Centre of St. Anne's University Hospital, Brno, Czech Republic) using capsules containing medical cannabis of Czech origin produced in the pharmacy of the aforementioned hospital.

Materials and Methods

Subjects and treatment procedure

The presented study involved 20 patients who were treated in the Centre for Pain Management at St. Anne's University Hospital, Brno, Czech Republic (Table 1). Patients had documented long-term therapy with medical cannabis, and all had been using it regularly for the treatment of chronic pain for at least 1 month at stable doses of either 62.5 mg orally, 1× a day in the evening, or 125 mg orally, 1× a day in the evening.

Table 1. Structure of the treatment groups.

Characteristics	n_1=10	n_2=10	*P*-value
Sex (F)/n (%)	7 (70 %)	5 (50 %)	0.65
Age/mean (std)	55.3 (7.9)	59.9 (12.8)	0.346
BMI (kg/m^2)/mean (std)	23.9 (4.6)	28.8 (3.7)	0.017

Abbreviations: F – female, std – standard deviation, BMI – body mass index.

Subjects were divided into two groups, each of 10 patients. The first group (n_1=10) was treated with the dose of 62.5 mg of cannabis (gelatin capsules) in the evening; the second group (n_2=10) was treated with the dose of 125 mg of cannabis in the same regime of administration (the same doses which were used for previous treatment of their painful conditions). Subjects were monitored over a precise time range 0-12 h.

In all subjects the amount of THC was assessed. THC was evaluated *via* saliva, and its accurate value was also estimated by blood analysis. The individual collections of biological material for blood analysis were carried out before dose administration and then after 6, 7, 8, 9, 10, and 12 h. For the saliva analysis, samples were taken before dose administration and then after 6, 9, and 12 h. Assessment of THC in saliva was carried out in the Clinical Pharmacology Unit of the ICRC. Blood was collected in the same facility, and, following transfer, THC levels were assessed using gas chromatography/mass spectrophotometry in the Department of Forensic Medicine (St. Anne's University Hospital, Brno). Patients were instructed and signed informed consent. The study protocol vas approved by the State Institute for Drug Control and by the Ethical Committee of St. Anne's University Hospital. Study was reported to the system EudraVigilance (EudraCT number 2019-003708-11).

Medical cannabis and preparation of hard capsules

Cannabis was supplied to the pharmacy in the form of dried female flowers (Elkoplast Slušovice s.r.o.). The content of THC in this plant material was 17.2 % and content of CBD less than 0.1 % and these concentrations were identical throughout the whole experiment. Besides from THC and CBD, carboxylated forms (tetrahydrocannabinolic acid, THC-A, and cannabidiolic acid, CBD-A) are also present in significant quantities in raw plant material. Therefore, in order to increase the effect of oral ingestion, the first step involved cannabis decarboxylation. Decarboxylation was carried out using a sterilization procedure: temperature 121 °C for 30 min. After this, the material was allowed to cool down. Cannabis was then treated in a splintery grinder and homogenized. Following homogenization, adjuvant substances were added (filling mass such as lactose or starch), and finally the required volume was produced. This mass was subsequently adjusted to gelatinous capsules. The amount of dried cannabis was 62.5 mg and 125 mg per capsule, respectively.

Determination of THC

Assessment of THC in saliva was performed by the test DrugWipe 5 SP (Securetec Detektions-Systeme AG, Neubiberg, Germany). It is described by its producer as an immunological quick screening test. The sample collector transfers the sample of saliva to the test strips, which contain drug-specific antibodies. If the saliva contains THC, they bind to the antibodies. The test was evaluated visually (in case of positivity, the test line turns red). This test is identical to the test used by the Police of the Czech Republic for routine controls of drivers. The test is negative at the THC level 0 ng/ml.

Evaluation of THC in blood was based on gas chromatography/mass spectrophotometry (GC-MS); the devices Finnigan TRACE GC Ultra and Finnigan PolarisQ (Thermo Electron Corporation, USA) were used. The lower limit of quantitation was 2 ng/ml. Quality control (QC) samples were prepared by spiking blank saliva and blank plasma samples obtained from healthy volunteers (blank pooled samples from 8 donors) with stock solution of THC.

Statistical analysis

Data are represented as mean and standard deviation (STD) if continuous, and as percentage and number of observation if categorical. The Fisher test is used for hypothesis testing of Binomially distributed variables, and the two-sample *t*-test for continuous normally distributed variables. The significant level alpha of 0.05 has been used for all statistical tests. The statistical software SAS has been used for all analysis.

Results

In the part of the study which involved assessment of THC levels in saliva the results were very consistent; the tests detected zero levels in all subjects following administration of both doses and at all time intervals after administration. The saliva data is not shown.

Assessment of THC levels in blood, however, revealed positive findings in one subject 9 h after administration of the lower dose, 4.5 ng/ml of THC (Table 2). In one patient who was given a higher dose, detectable levels of THC occurred 6 and 7 h after administration, 2.4 ng/ml and 3.8 ng/ml respectively (see Table 2). Interestingly, we found that two patients showed positive results even in blood samples collected prior to the experimental medical cannabis

Table 2. Levels of THC in blood serum (ng/ml) in estimated time intervals during 12 h after medical cannabis (62.5 mg and 125 mg, respectively) oral administration.

Patient (62.5 mg)	**b.a.**	**6 h a.a.**	**7 h a.a.**	**8 h a.a.**	**9 h a.a.**	**10 h a.a.**	**12 h a.a.**
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0
8	0	0	0	0	**4.5**	0	0
9	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0
Patient (125 mg)	**b.a.**	**6 h a.a.**	**7 h a.a.**	**8 h a.a.**	**9 h a.a.**	**10 h a.a.**	**12 h a.a.**
11	0	**2.4**	**3.8**	0	0	0	0
12	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0
17	**4.6**	**4.7**	**4.2**	**3.9**	**4.1**	0	0
18	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0
20	**2.7**	**11.5**	**6.9**	**6.2**	**6.3**	**2.8**	0

Results are expressed as absolute values. Abbreviations: b.a. – before administration, a.a. – after administration.

administration. This is a rather unexpected finding, and we ascertained, that these two patients had used a cannabis dose in the time before they started to be under our control (4.5 h before the administration for experimental purposes). This issue will be discussed in the next section of this paper.

Discussion

It has been well documented, at first particularly in association with recreational use, that cannabis impairs psychomotor skills, concentration, problem-solving and cognitive functions (including reaction time), which consequently affects driving abilities and therefore compromises driving safety. The following few examples represent the effects of cannabis on driving and may be considered typical. Bondallaz with colleagues in their review [34] presented results showing cannabis-induced impairment of actual driving performance in the forms of increased lane weaving and mean distance headway to the preceding vehicle. Moreover, they reported that both acute and long-term dose-dependent impairments of specific cognitive functions and psychomotor abilities were also seen even a few weeks following the cessation of cannabis use. Drivers influenced by cannabis multiplied their risk of being responsible for causing a fatal accident by 1.65 (1.16±2.34); odds ratio with 95 % confidence intervals [35]. Research carried out with healthy occasional users of cannabis who were tested to see the effects of different types of cannabis on lane weaving using a standard deviation of lateral position (SDLP) revealed that the SDLP following vaporized THC-dominant and THC/CBD-equivalent cannabis was significantly greater as compared to placebo at 40 to 100 min but not at 240 to 300 min after vaporization [36]. For similar results see [37-39]. Based on these references, it can be unambiguously concluded that cannabis consumption (for any reason) may impair the ability to drive and prescribing physicians must take this into account.

Levels of THC in the blood affect driving abilities in a dose-dependent manner, and different

THC blood levels are tolerated within Europe. In many countries, a zero-tolerance approach is applied, possibly due to the set of low cut off level in the blood, which is close to the limit of quantification in most analytical methods, and there is no necessity of assessing behavioral impairment.

In the Czech Republic, where this study was conducted, the zero-tolerance approach is applied, and according to the directive of the Supreme Public Prosecutor's Office No. 5/2019, a level above 2 ng/ml is considered the cut-off for cannabis-impaired driving. Levels above 10 ng/ml while driving are considered a criminal offense, and drivers may be imprisoned. The court mostly relies on expert opinion.

Our results were obtained using the LC-MS method from blood serum of real patients who have been administered cannabis regularly for at least 1 month at stable doses to treat chronic pain. In the group of subjects who were given medical cannabis within the experiment at the dose of 62.5 mg, a THC level exceeding 2 ng/ml was seen 9 h after administration only in one case (No. 8; 4.5 ng/ml). There were no traces of THC one hour later in this particular patient, and zero levels were seen generally in all other cases in this group even six hours following drug administration. Similarly, in the group of subjects who were given higher doses of medical cannabis (125 mg), one patient showed a THC blood level above 2 ng/ml 7 h after administration (No. 11; 3.8 ng/ml), and at non-detectable levels one hour later. As with the group that was administered lower doses of cannabis, zero levels of THC were found in all other patients apart from patients No. 17 and No. 20 respectively. However, as we admitted above, these two patients had detectable baseline THC levels in the blood due to cannabis intake before the administration of our experimental doses. On one hand, these two subjects decreased the number of patients who were given cannabis in accordance with the experimental design; on the other hand, they documented that, despite having positive values as baselines, even in these cases zero THC levels were found in either of them after 10 and 12 h respectively.

Moreover, various factors, which may influence absorption of THC may be poorly controlled in the clinical setting, even in our clinical trial. These factors may include the influence of meal (fatty, fibre-rich), co-medication (spasmolytics, laxatives, prokinetics, antiemetics) which may also modify the GIT motility and thus THC absorption. Besides these, as described above, CYP2C9, CYP2C19 and CYP3A4 play significant role in THC metabolism. It is well known that CYP2C9 and CYP2C19 are polymorphic enzymes and therefore in carriers of mutant alleles CYP2C9*2 (c.430C>T, p.R144C) and CYP2C9*3 (c.1075A>C, p.I359L) may lead to decreased enzyme activity and phenotype of poor metabolism and thus prolonged half-life [40]. CYP2C19 is also a polymorphic enzyme, while all CYP enzymes responsible for THC metabolism may be under influence of inhibitors or inducers. These factors may be hardly controlled and may contribute to high variability in THC absorption and metabolism.

Although the pharmacokinetics of THC is relatively well known, and the use of cannabis for medical purposes is an increasing trend and now legal in many countries, there is a considerable lack of information about how much time must elapse from an individual's last cannabis dose to ensure safe driving and THC levels in the blood in accordance with the valid legal rules. One of the very few reports which can be found with respect to a safe time-frame for driving after cannabis administration recommends that patients should not drive for at least 8 h after achieving a subjective "high" from self-treatment with smoked marihuana [41]. This can be compared to our findings just to a limited extent, as the route of administration (inhalation) was different from our experiment (oral); nevertheless, it was also clearly seen in our patients that there were no THC levels detectable 10 h after use (among all subjects who met the criteria of the correct experimental design), which is at least similar to the conclusions of the authors above.

The College of Family Physicians of Canada has recommended to patients prescribed medical cannabis not to drive for at least 4 h after inhalation, 6 h after oral ingestion, and 8 h after inhalation or oral ingestion if the patient experienced euphoria [42]. Comparing this suggestion to our results, it can be seen that a large majority of our patients (with zero levels of THC in their blood before the first cannabis dose) also showed zero levels six hours after administration (16 of 18).

Interestingly, results obtained from the part of study which estimated THC in the saliva revealed zero levels in all patients at all-time intervals, even in the 2 subjects who had positive levels already as their baseline. This speaks in favor of the hypothesis that the sensitivity and reliability of the test used is not satisfactory for its intended purposes.

Taken together, numerous studies have demonstrated that administration of cannabis is

associated with a significant risk of impaired cognition and psychomotor performance. This is, however, an adverse effect commonly seen with a large number of other drugs commonly used at the present time for various indications (e.g. benzodiazepines, "z-hypnotics", sedative antidepressants, opioids, neuroleptics) [43-47].

Cannabis has beneficial effects in many patients, particularly for the management of chronic pain [48-50], and there is increasing interest in its use for these purposes. At the beginning of therapy with cannabis, the physician must inform patients of any possible adverse effects associated with the treatment, including possible effects on their ability to drive or operate machinery safely, and of THC limits in their blood that can carry a risk of impaired driving as well as violating legal norms.

According to our knowledge, there is lack of reliable data dealing with this issue. It has been described that plasma level of THC dropped below 2 ng/ml following 6 h after intravenous administration. After smoking of a cannabis cigarette (containing about 16 mg of THC) the concentrations below the detection limit of 0.5 µg/l was observed after 7.2 h; with a cigarette containing about 34 mg of THC the levels below limit of quantification was reached within 12.5 h [51].

Thus, despite the aforementioned limitations, the major contribution of our study lays in its estimation of blood THC levels following administration of routinely used doses and routinely used drug dosage form of medical cannabis and so the results of this study may be reflected in recommendations which are given to the real patients who have been using medical cannabis in the context of chronic pain management.

Conclusions

The legal use of cannabis for medical purposes was not possible for decades, but it has become legal again in many countries throughout the world. Increasing attention is now being paid to the use of medical cannabis for several indications, especially for the treatment of chronic pain, resistant to "classical" analgesic drugs. Administration of cannabis is similar to other commonly used drugs also associated with some adverse effects, including impaired driving ability, and it is therefore necessary for physicians to know a time, that can be recommended to patients as a sufficient interval for safe driving after their last dose of cannabis. Hence, this study evaluated blood concentrations of THC at predefined time intervals after medical cannabis oral administration and assessed the time needed for THC levels to decline below 2 ng/ml, which is the estimated level to ensure legal driving. Based on the patients involved in this study, who exhibited THC levels above the aforementioned value, our finding suggested that for an unaffected ability to drive, at least 9-10 h should elapse from the last cannabis use. We strongly believe that presented study can lay foundation for further and more elaborate study which can have deep socio-medical impact.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Financial support for the conduct of the research and/or preparation of the article was provided by the European Regional Development Fund – Project ENOCH (No. CZ.02.1.01/0.0/0.0/16_019/0000868) and by the state budget by the MEYS, large infrastructure project CZECRIN (No. LM2018128), within activity Project of the large infrastructures for R&DI. Proofreading of the manuscript was performed by Mr. Evan McElravy.

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