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Tetrahydrocannabinol in Pediatrics: Room for Improvement?

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Keywords
Medical cannabis · Δ9-tetrahydrocannabinol · Pediatrics · Evaluation · Patient safety · Palliative care

Abstract

Introduction: The use of medical cannabis in pediatrics is not common in clinical practice, and there is a lack of prospective studies, especially in pediatric subpopulations. This study aimed to provide data on the off-label administration of tetrahydrocannabinol (Δ9-THC) in a pediatric tertiary center in Austria. ***Methods:*** A retrospective data analysis was performed to assess the use of Δ9-THC at the Department of Pediatrics and Adolescent Medicine at the Comprehensive Center of Pediatrics (Medical University Vienna) from 2016 to 2018. The use of Δ9-THC in the Pediatric Department at the Medical University Vienna between 2016 and 2018 was analyzed using a retrospective design. ***Results:*** The most common diagnoses of patients receiving Δ9-THC were brain cancer and genetic diseases, including inborn metabolic disorders. The 32 patients who had received Δ9-THC had an arithmetic mean of 9.42 diagnoses and were treated with an arithmetic mean of 13.52 other drugs. Eleven of the 32 patients died by the end of the study period, indicating palliative use. ***Conclusion:*** The data shows that only severely ill patients were treated with Δ9-THC. A lack of information on the drug's indications, duration, and dosage was noticed in the files, which could represent problems for patient safety.

Introduction

The discovery of endocannabinoids in the 1990s facilitated insight into substances produced by the human body that can bind to cannabinoid receptors. At least five different endocannabinoids have been discovered, of which the most researched are anandamide and 2-arachidonoylglycerol [1]. This milestone has highlighted the role of endocannabinoids in physiological and pathological processes in the entire human body, making them a promising target for novel therapeutic approaches in conditions such as epilepsy [2], Tourette syndrome [3], anxiety disorders [4], attention deficiency/hyperactivity disorder [5], and autism spectrum disorder [6]. Registered cannabinoids for medical purposes approved by the US Food and Drug Administration (FDA) are cannabidiol (CBD), Δ9-tetrahydrocannabinol (Δ9-THC)-analogs, dronabinol and nabilone, and a combination of both, nabiximols [7]. Cannabis has been administered to

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children for indications such as epilepsy, pain, and nausea, previously validated in older age groups [8, 9]. These historical uses reflect the enduring recognition of their efficacy in addressing various medical conditions and provide a strong foundation for further exploration and development in the field. However, regarding the use of cannabinoids in pediatrics, there are limited data available, and valid information on indications and frequency of use in pediatric settings is sparse. Some other indications for CBD seem promising but need randomized controlled trials (RCTs) before they can be prescribed in clinical routine. Nevertheless, several children receive cannabinoids in specific clinical situations [10, 11] based on individual therapy decisions (off-label use). In addition to it, Δ9-THC finds use primarily in pediatric palliative settings [12].

In adults, a moderate effect for the treatment of spasticity is described [13]. Furthermore, Δ9-THC is administered in patients with chemotherapy-associated nausea and vomiting [13, 14] and shows an effect in chronic and neuropathic pain patients [15, 16].

So far, evidence for the reported effects of cannabinoids is moderate to low-quality [14, 17]. Selective reporting, incomplete data, small sample sizes, and inadequate descriptions of methods currently limit the available evidence [14, 17]. More structured prospective studies, such as RCTs or patient registers, are needed to confirm reported effects, specifically in pediatric populations [13, 14].

Although the available evidence is limited, Δ9-THC finds use in pediatric clinical settings. The primary objective of this analysis was to evaluate the magnitude of the use of Δ9-THC in pediatric tertiary care in Austria, represented by the general hospital of Vienna as the biggest pediatric center in Austria.

Materials and Methods

A retrospective design was applied to provide information on the administration of off-label use of Δ9-THC. After approval of the Ethics Committee of Vienna's Medical University (No. 2001/2019), data on all Δ9-THC orders of all pediatric departments at the Comprehensive Center of Pediatrics between 2016 and 2018 were provided by the hospital's pharmacy. All patients who received Δ9-THC as an oral solution (dronabinol drops) from January 2016 to December 2018 were included. Parameters of interest included age, weight, gender, dosage and dosing titration, number and type of diagnoses, and concomitant medications. The information was extracted from the documentation on narcotic drug orders, patients' medical history as documented in an electronic documentation system, and hand-written liaison reports. The parameters of interest were collected in a pseudonymized file. All data were analyzed using IBM SPSS Statistics 25.

Table 1. Overview of main diagnoses

Main diagnoses	*n*	%
1 Neoplastic diseases	9	28.1
2 Genetic diseases	7	21.9
3 Autoimmune diseases	7	21.9
4 Diseases of cardiovascular system	4	12.5
5 CNS malformations	2	6.3
6 Psychiatric diagnoses	1	3.1
7 Accidents	1	3.1
8 No primary diagnosis provided	1	3.1

The data were saved and archived on a computer with restricted access at the Medical University of Vienna. All statistical analyses were done on a computer with limited access at the Medical University of Vienna.

Results

Of all approximately 4,000 inpatient contacts and approximately 59,000 outpatient contacts per year between January 2016 and December 2018 at the Department of Pediatrics of Comprehensive Center Pediatrics Vienna, 32 hospitalized patients were identified and included that received Δ9-THC.

Characteristics

A total of $n = 32$ patients were evaluated. Age ranged from 2.10 years to 21.1 years. The patients older than 18 years were still treated at the pediatric department due to the chronic character of their diseases. Therefore, their data were included.

The reported weight of the patients, retrieved at admission, ranged between 13.00 kg and 61.50 kg. Three files lacked body weight documentation; hence, the weight of the three respective patients could not be included.

Main Diagnoses

The total number of diagnoses per patient varied from 1 to 34, with a mean of 9.42 (standard deviation [SD] = 6.68) and a median of 8 (interquartile range [IQR] = 7). One patient's diagnosis was not documented. The reported primary diagnoses were neoplastic, inborn, and autoimmune diseases. Table 1 gives an overview of the primary diagnoses. All the cancer diseases in category 1 included brain cancers (medulloblastoma, malign germ cell tumor, anaplastic ependymoma, ponsglioma, diffuse glioma, and chondroma of the skull base). Category 2 (genetic diseases) included cystic fibrosis, mitochondriopathy, CLOVES syndrome, MPV-associated hepato-cerebral

Table 2. Indications for Δ9-THC

Indications	*n*	%
1 Aggressive behavior	1	2.6
2 Anorexia	1	2.6
3 Compliance reasons	1	2.6
4 Delirium	1	2.6
5 Dysthymia	1	2.6
6 Violent outbursts	1	2.6
7 Tic-associated vomiting	1	2.6
8 Anxiety	2	5.1
9 Depression	2	5.1
10 Pain	2	5.1
11 Sleeping disorders	2	5.1
12 Loss of appetite	3	7.7
13 Analgesic withdrawal	3	7.7
14 Palliative setting	4	10.3
15 No indication provided	14	35.9

Table 3. Concomitant medication administered in number of patients

Concomitant medication	*n*	%
1 Gastrointestinal drugs	27	87.1
2 Analgesics	25	80.7
3 Artificial nutrition	22	71.0
4 Immunomodulators	21	67.7
5 Anti-infectives	20	64.5
6 Sedatives and muscle relaxants	17	54.8
7 Cardiovascular drugs	15	48.4
8 Electrolytes	15	48.4
9 Anticonvulsant drugs	13	41.9
10 Psychotropic drugs	11	35.5

mitochondrial DNA depletion syndrome, and mucopolysaccharidosis III. Summarized diseases in category 3 were Crohn's disease, Wegener granulomatosis, juvenile dermatomyositis, focal segmental glomerulosclerosis, seronegative juvenile polyarthritis, and Hurst encephalitis. Category 4 consisted of a patient after heart transplantation, dilatative cardiomyopathy, and situs inversus with dextrocardia. In category 5, CNS conditions excluding tumors were summarized: bleeding of an angioma and a congenital arachnoidal cyst. Categories 6 and 7 consisted of tic-induced vomiting and skin scalding after a combustion accident. No primary diagnosis could be retrieved from the medical records in one case.

Δ9-THC Use

Twelve files kept no record of the duration of treatment with Δ9-THC. The treatment period with Δ9-THC in 20 patients was between 1 and 111 days (mean = 28.20, SD = 31.40; median = 22, IQR = 32). At the endpoint of data collection, one patient was still treated with Δ9-THC. In 26 patients (81.3%), Δ9-THC was not reported as an ongoing medication. There was no information on any medicine available in 5 patients.

Indications for Δ9-THC

Of the 19 patients (59% of the complete sample) whose records included indications, 21% ($n = 4$) were treated with Δ9-THC in a palliative context. Other indications for the Δ9-THC treatment were the following: analgesic withdrawal ($n = 3$, 16%), loss of appetite ($n = 3$; 16%), sleeping disorders ($n = 2$; 11%), pain ($n = 2$; 11%), depression ($n = 2$; 11%), anxiety ($n = 2$; 11%), tic-associated vomiting ($n = 1$; 2.6%), violent outburst ($n = 1$; 5%), dysthymia ($n = 1$; 5%), delirium ($n = 1$; 5%), compliance reasons ($n = 1$; 5%), anorexia ($n = 1$; 5%), and aggressive behavior ($n = 1$; 5%). For 13 patients (41%), no indication for the Δ9-THC prescription could be found. The total number of indications ($n = 39$) is higher than the number of patients with a documented indication ($n = 19$) because, for most patients, more than one indication was reported. Table 2 gives an overview of the indications for Δ9-THC as reported (sorted from less frequent to most frequent).

Concomitant Medication

Of all patients included, 31 (96.9%) received concomitant medication. In one patient (3.1%), no medical record on other medicines could be found. For the 31 patients whose concomitant medication was reported, the number of drugs ranged from 3 to 26 (mean = 13.52, SD = 6.41; median = 12, IQR = 11). Table 3 gives an overview of the ten most prescribed groups of drugs during hospitalization.

Dosing of Δ9-THC

The dosing of Δ9-THC varied widely. Minimum dosage per day reached from 0.83 mg/d to 8.33 mg/d (mean = 2.61, SD = 2.02; median = 1.67; IQR = 1.73) corresponding to 0.02 mg/kg/d to 0.2 mg/kg/d (mean = 0.43, SD = 0.37; median = 0.37; IQR = 0.413). Maximum dosage per day reached from 1.67 mg/d to 23.32 mg/d (mean = 10.78, SD = 7.04; median = 9.996; IQR = 13.27) corresponding to 0.03 mg/kg/d to 1.8 mg/kg/d (mean = 0.08, SD = 0.05; median = 0.06; IQR = 0.07). The prescribing information on Δ9-THC provided by the FDA suggests 20 mg/d as the maximum dosage in adults [18]. The results show a great variation in dosing. The maximum daily dosage of 23.32 mg/d was administered to a 3.8-year-old with consecutive heart transplantation.

Discussion

This study aimed to evaluate the use of Δ9-THC in an Austrian pediatric tertiary care center from 2016 to 2018, focusing on indications and patient characteristics. 32 patients were identified in total who received Δ9-THC. Those patients had a mean of 9.42 diagnoses and a median of 8 diagnoses and were treated with a mean of 13.52 (median: 12) other drugs. The most common diagnoses were brain cancer and genetic diseases, including inborn metabolic disorders. These characteristics indicate that most patients receiving Δ9-THC in our sample were severely ill, multimorbid children, and adolescents. Throughout the treatment, 11 of the 32 patients died, marking the use in a palliative setting. Considering the indications for Δ9-THC, only chronic pain turned out to be a reported indication with available evidence from systematic reviews [14] supporting its use in chronic pain management. Four patients (12.5%) received Δ9-THC for appetite stimulation or anorexia, which is stated at least as an indication in adult AIDS patients according to the prescribing information [19]. However, it is important to note that the available evidence for these indications primarily pertains to adult populations.

A notable limitation of this retrospective analysis is the lack of reported side effects or adverse events because structured documentation were available. Furthermore, the varying number of concomitant medications in the sample limited the ability to report on side effects. In the literature, commonly described adverse effects of Δ9-THC included fatigue, changes in appetite, and vomiting [19]. Additionally, in palliative settings, apnea and hypopnea have been reported [19]. Concerning side effects, children are a particularly vulnerable population. Children exhibit a higher risk for severe neurobehavioral side effects compared to adults when used recreationally [20]. Safety data from RCTs state relatively few and non-severe adverse events such as somnolence, weight loss, and increased liver transaminases for the use of CBD. The safety profile regarding the use of CBD in pediatric populations remains relatively understudied. Limited studies conducted on the use of THC in small children have shown no serious treatment-related adverse events [6].

This analysis provided no information on the therapeutic effects of Δ9-THC due to the lack of reported outcomes in patients' records. Therefore, the retrospective nature of this study inherently limits the data's validity and limits a comprehensive understanding of treatment efficacy. This emphasizes the crucial need for adequate and standardized documentation to ensure patient safety, especially in the context of Δ9-THC administration to pediatric populations.

In sum, the results highlight the current landscape of Δ9-THC treatment in pediatric patients and emphasize the importance of data availability and adequate documentation of critical data in medical records (e.g., dose, duration, and indication for Δ9-THC treatment) in consideration of patient safety, especially with the use of Δ9-THC in a pediatric population. As already demanded by various authors, prospective studies in a pediatric setting to evaluate the effects and side effects of medical cannabinoids in different subpopulations are urgently needed. In this regard, RCTs remain gold standard, but contain great challenges when conducting multi-compound plant substances, such as cannabis. Observational studies and patient registers obtain the immense potential of a structured evaluation of the utilization of cannabinoids in pediatric populations and could prepare valuable data with a more robust evidence base and could form a deeper understanding of the potential of cannabinoids in pediatric patients and leading to improved patient care and safety.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Ethical Committee of Vienna's Medical University (No. 2001/2019). Due to retrospective data analysis, no written informed consent was required and was not performed after approval by the Ethical Committee of Vienna's Medical University (see above).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, C.D. and C.K.; formal analysis, P.S., R.S., and C.D.; investigation, C.D. and P.S.; writing – original draft preparation, C.D., C.K., and P.S.; writing – review and editing, C.K., R.S., C.S., and C.D.; supervision, C.K.; and all authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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