Marijuana Misadventures in Children
Exploration of a Dose-Response Relationship and Summary of Clinical Effects and Outcomes

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Objectives: This study aimed to explore a dose-response relationship of delta-9-tetrahydrocannabinol (THC) in THC-naïve children after unintentional acute exposure and compare clinical outcomes with non-naïve children.

Methods: A retrospective review was performed on children aged 31 days to 20 years who presented to Children's Hospital Colorado for care related to acute THC toxicity. The children were divided into groups based on exposure: group 1 (THC naïve) and group 2 (THC non-naïve).

Results: A total of 38 children (age, 3.5 [3] years) met inclusion for group 1 and an equal number of children (age, 15.1 [3.9] years) met the criteria for comparison in group 2. Eight naïve patients had documentation of estimated THC dose ingested (mean [SD], 7.13 [5.8] mg/kg; range, 2.9–19.5 mg/kg). A direct relationship between estimated oral THC dose, level of medical intervention required, and hospital disposition was observed. Lethargy/somnolence was more common in the naïve group (84% vs. 26%, $P < 0.0001$) whereas problems in cognition, perception, and behavior were more common in the non-naïve group (4% vs 11%, $P = 0.01$). The duration of clinical effect and length of hospital stay were longer in the naïve group (19.3 vs 5.0 hours, $P < 0.0001$) and (0.73 vs 0.19 days, $P < 0.0001$) respectively.

Conclusions: There seems to be a direct relationship between the estimated oral THC dose (mg/kg), hospital disposition, and level of medical intervention required. Symptoms and duration of effects after THC exposure varied based on the route of exposure, age of patient, and history of previous THC experience.

Key Words: marijuana, delta-9-tetrahydrocannabinol, pharmacology, toxicology

(*Pediatr Emer Care* 2018;34: 457–462)

Background

Cannabis sativa or *Cannabis indica* has been used recreationally and medicinally for centuries.[1,2] Cannabis contains numerous cannabinoids, including delta-9-tetrahydrocannabinol (THC), which is responsible for the psychoactive effects.[3] The THC is consumed through ingestion (eg, edibles, liquids) or inhalation (eg, smoking, vaporizing).[4] Although commonly considered a compound resulting in relaxation and euphoria, ingestion of a single oral dose of THC in adults has been associated with acute anxiety, panic reactions, and psychotic symptoms. These activating symptoms are more likely in naïve users compared with chronic users.[5] The pediatric population can also exhibit more significant symptoms such as coma and respiratory depression. In addition, there are serious unpleasant dose-related effects such as tachycardia and respiratory depression that have been reported with acute toxicity.[1,6–11]

Importance

According to the US Drug Enforcement Administration, marijuana is a schedule I controlled substance and thus cannot be legally prescribed under federal law. Marijuana and other THC-containing products, however, are now available in several states in both medical and recreational form, including Colorado.[12] Although recreational use of marijuana has increased, so too has the number of unintentional ingestions and acute toxicities in children.[12,13] According to a recent Centers for Disease Control and Prevention report, more high school seniors are choosing marijuana over alcohol or tobacco.[14] In addition, the commercialization of marijuana has been associated with a lower risk perception among users.[15] As the rate of THC use, abuse, and availability increase, clinicians will need to be prepared to identify and manage infants and children with acute intoxication. As other states enact laws legalizing medical and recreational marijuana, exploration of the relationships between dose and response will become more relevant.

Goals of This Investigation

The specific aims of this study are to explore the possibility of a dose-response relationship in THC-naïve children and to compare clinical symptoms and outcomes to THC–non-naïve children after THC exposure. Although dose-response relationships have been described in adults who consume THC,[10,16] the influence of tolerance after repeated THC exposure can confound conclusions. However, THC-naïve children represent a unique model that removes the influence of cannabinoid receptor tolerance and allows for a more precise dose-response relationship determination.

METHODS

Study Design and Setting

This was a retrospective chart review of children, aged 31 days to 20 years, admitted to our local children's hospital between November 1, 2009 and December 1, 2014 with an International Classification of Diseases-Ninth Revision code of 305.20 (Cannabis Abuse, Unspecified Use), 969.6 (Poisoning by Psychodysleptics [hallucinogens]), and E854.1 (Accidental Poisoning by Psychodysleptics [hallucinogens]). Our hospital is a university-affiliated, freestanding, tertiary care children's hospital and level I trauma center with an annual emergency department patient census of more than 70,000. The specific study period was selected in an effort to reflect changes in Colorado's drug enforcement landscape and prosecutorial focus, and when previous reports of pediatric exposures have been described.[17,18] At the start of the study period, federal fiscal resources previously devoted to cannabis cases were redirected and laws were modified to reduce the prosecution of medical marijuana cases.

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Disclosure: The authors declare no conflict of interest.
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Presented at the Pediatric Pharmacy Advocacy Group Annual Meeting: Marijuana Misadventures in Children: Exploration of a Dose-Response Relationship, April 2015, Minneapolis, MN.

ISSN: 0749-5161

TABLE 1. Characteristics of Patients Meeting Eligibility Criteria After Presenting to the Children's Hospital Emergency Department for Management of Acute Marijuana (THC) Intoxication

Characteristics	THC Naïve (n = 38)	THC Non-Naïve (n = 38)	*P*
Age, y	median, 3.1	median, 15.2	<0.0001
	3.5 (3.0)	15.5 (3.1)	
	0.67–15.1	1.9–19.9	
Male sex, n (%)	21 (55)	25 (66)	0.48
Weight, kg	median, 14.2	median, 56.6	<0.0001
	16.3 (9.3)	57.2 (12.9)	
	8.4–52.2	14.5–90.7	
Ethnicity, n (%)			
White	19 (50)	10 (26)	0.06
Hispanic/Latino	11 (29)	15 (39)	0.46
African American	7 (18)	9 (24)	0.78
Asian	1 (3)	0 (0)	1.0
Other	0 (0)	4 (11)	0.12

Data are presented as mean (SD) (range) or percentage, as appropriate.

Children were excluded if they had confirmed concomitant exposure to other substances (eg, THC plus ethanol or other licit/illicit drugs) or if their positive THC urine screen finding was incidental to their admission and not the primary reason for seeking care. Children meeting the inclusion criteria for a detailed review were then divided into 2 groups based on exposure. Group 1 consisted of THC-naïve children treated for unintentional exposure, and group 2 consisted of an equal number of THC–non-naïve children treated for acute toxicity. An *unintentional exposure* was defined as an acute, inadvertent ingestion of THC in a first-time user. *Toxicity* was defined as an acute ingestion/inhalation of THC in a THC–non-naïve individual whose intent was to consume THC, but the experience resulted in an unexpected or undesirable consequence or symptom. This study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board with a waiver of informed parent/subject consent.

Outcome Measures

The following data were collected and reviewed: (i) patient information: sex, age, weight, and medication history and (ii) marijuana exposure information: symptoms/clinical effects, duration of effect, hospital disposition, length of stay, and type of THC product consumed (name, dose [milligrams of THC], and route of exposure). Using medical outcome categories defined by the American Association of Poison Control Centers,[19] we classified clinical effects based on the level of medical intervention required, as follows: (i) mild effects were those perceived to be minimally bothersome and that resolved rapidly, (ii) moderate effects were those that required some form of medical treatment but were not life-threatening or resulting in prolonged disability (eg, required intravenous fluids), and (iii) severe effects (also known as major effects) were those that resulted in life-threatening symptoms and required intensive care treatment/support (eg, seizures, hemodynamic instability, and respiratory distress).

Primary Data Abstraction and Analysis

Outcome measures and variables were extracted from charts by 3 investigators using a standardized data collection form. To improve accuracy and minimize inconsistencies, all charts underwent a second data abstraction by a different investigator. Periodic meetings were held to discuss issues with data extraction, and any disputes in chart coding were resolved after agreement by all investigators. A descriptive analysis was performed on each variable in the data set. Results are presented as mean (SD) and range, or percentage where appropriate. Medians are reported if significant skewing of the data was observed. A 2-tailed *t* test, Fisher exact test, and 1-way analysis of variance were used to detect differences between the patient groups. Data were graphed using GraphPad Prism version 6.00 for Mac OS X (GraphPad Software, La Jolla California) and Microsoft Excel version 2010 for Mac OS X (Microsoft Software, Redmond Washington) software.

RESULTS

Characteristics of Study Subjects

Initial data retrieval identified 2287 patients with an International Classification of Diseases-Revision code consistent with cannabis abuse or poisoning. After exclusion for coingestions or exposures, age limits, and admissions not related to positive THC, 38 children (age, 3.5 [3] years) met inclusion for unintentional exposure (group 1), and an equal number of children (age, 15.5 [3.1] years) with acute toxicity met the criteria for comparison (group 2). The specific patient demographics are listed in Table 1. There was a male predominance in both groups (55% and 66%, respectively). There was a significant difference in age and weight between the 2 groups.

Main Results

The elements of THC exposure are described in Table 2. The THC-naïve patients were more likely to have oral THC exposures from edible products (66% vs 13%, $P < 0.0001$), whereas THC–non-naïve patients were more likely to have inhaled exposures from smoking marijuana (84% vs 8%, $P < 0.0001$). The types of edible products consumed are shown in Figure 1. The determination of dose was also different between groups, with the THC-naïve population being more likely to have an estimated dose reported from the exposure (26% vs 5%, $P = 0.025$). Although clinical symptoms related to THC exposure were recorded for all patients, only 10 naïve patients had documentation of the

TABLE 2. Elements of Marijuana (THC) Exposure Documented in the Medical Record Among Children Seeking Medical Attention for Acute THC Intoxication

	THC Naïve (n = 38)	THC Non-Naïve (n = 38)	*P*
Route of exposure, n (%)			
Oral	25 (66)	5 (13)	<0.0001
Unknown	10 (26)	1 (3)	0.0067
Inhaled	3 (8)	32 (84)	<0.0001
Type of product consumed, n (%)			
Unknown	15 (39)	1 (3)	0.0001
Marijuana buds	4 (11)	32 (84)	<0.0001
Edibles	19 (50)	5 (13)	0.0011
Time elapsed between THC exposure and presentation, h	6 (5.8) 1–22	2.9 (2.0) 0.5–9	0.0026
THC dose determination possible?, n (% yes)	10 (26)	2 (5)	0.025

Data are presented as mean (SD) (range) or percentage, as appropriate.

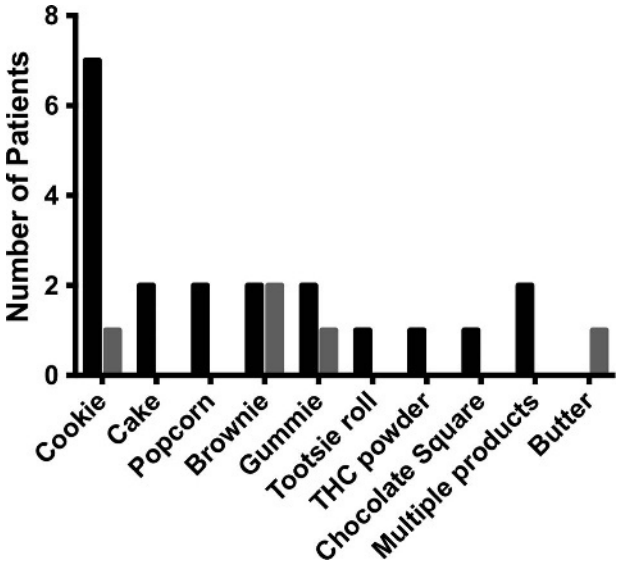

FIGURE 1. Summary of edible marijuana (THC) products consumed by THC-naïve patients (n = 19; black bars) and THC–non-naïve patients (n = 4; gray bars).

estimated active THC dose consumed. Of these 10 patients, 2 ingested raw marijuana buds which are thought to be devoid of characteristic effects without heat activation.[20,21] The relationships between estimated THC dose, hospital disposition, and medical intervention required in the remaining 8 THC-naïve patients are illustrated in Figure 2. Although there was substantial variability and some uncertainty in the reported dose of the exposure (mean [SD], 7.13 [5.8] mg/kg; range, 2.9–19.5 mg/kg) an apparent direct relationship between the dose ingested, level of medical intervention required, and hospital disposition was demonstrated (Fig. 2, panels A and B). The highest ingested doses resulted in admission to the intensive care unit. Children with an estimated oral THC exposure of approximately 3 mg per kilogram of body weight (or less) were likely to be observed within the emergency department and not require hospital admission. Admission to the hospital was more likely when naïve children ingested greater than 5 mg of THC per kilogram of body weight (Fig. 2, panel B).

Clinical symptoms experienced by members of the study groups after THC exposures are summarized in Table 3. The THC-naïve patients experienced significantly more lethargy or somnolence compared with THC–non-naïve patients (84% vs 26%, $P < 0.0001$). The THC–non-naïve patients reported a significantly higher number of symptoms related to cognition, perception, or emotional state and behavior (11% vs 4%, $P = 0.01$). Although not statistically significant, the incidence of respiratory insufficiency was higher in the naïve group and resulted in invasive/noninvasive respiratory support in 2 children. The mean duration of clinical effect was longer in THC-naïve patients (19.3 hours) compared with the THC–non-naïve group (5 hours, $P < 0.0001$). Overall, there were no statistically significant differences between groups for mild, moderate, or severe effects, with the majority of patients experiencing moderate effects and requiring some degree of medical intervention, namely intravenous fluids (Fig. 3).

Although the majority of patients in this study were naturally categorized into young naïve patients with edible exposures and non-naïve adolescent patients with inhaled exposures, we did have some notable outliers. Specifically, 1 young patient (aged 1.9 years) was classified as non-naïve after being repeatedly exposed to oral THC by his father to help abate agitation and abnormal movements, and 2 adolescent patients (aged 12.8 and 15.1 years) were classified as THC-naïve after they unknowingly consumed edible THC for the first time. In addition, we did have a small number of young patients exposed to THC via inhalation. Therefore, in an effort to explore the possibility of *independent* influence of age and route of exposure on clinical outcomes, we performed a secondary analysis. We compared inhaled exposures in young patients (younger than 10 years, n = 3) to that of inhaled exposures in adolescent patients (10 years or older, n = 32). The only significant finding was that adolescent patients were more likely to experience circulatory and respiratory symptoms than younger patients. (6% vs 2%, $P = 0.019$). In addition, we compared oral THC exposures in young patients (younger than 10 years, n = 24) to oral THC exposures in adolescent patients (10 years or older, n = 6) and found no significant differences in reported symptoms.

In terms of hospital disposition, significantly more THC-naïve patients were admitted to the pediatric intensive care unit (PICU) than THC–non-naïve patients (16% vs 0%, $P = 0.025$; Fig. 4). The length of hospital stay (days) was significantly longer

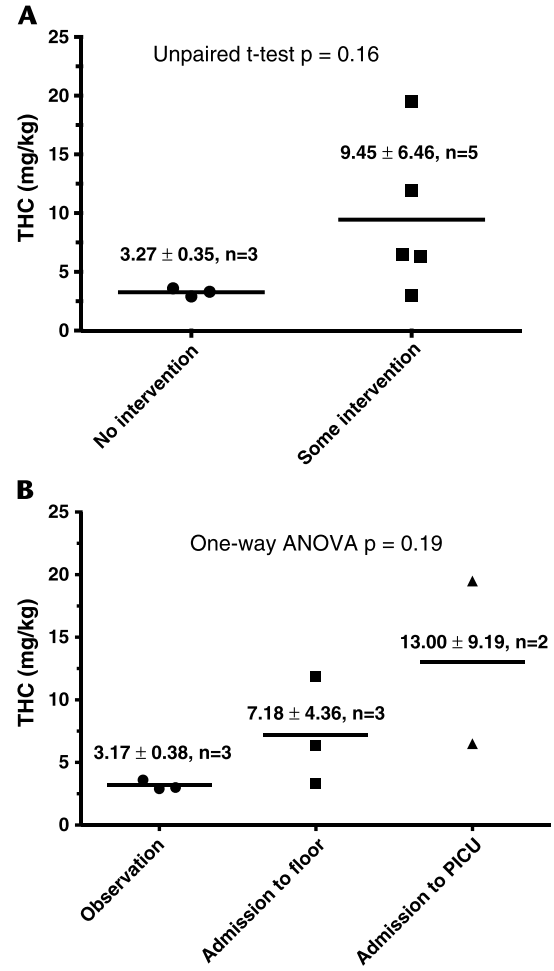

FIGURE 2. Relationship between estimated THC ingested (mg THC per kg weight of patient) and whether medical intervention was required (Panel A) and hospital disposition (Panel B) in 8 THC-naïve children who presented to the emergency department with acute THC intoxication.

TABLE 3. Summary of Clinical Symptoms Reported by and Observed in Children After Acute Intoxication With THC

	THC Naïve (n = 38)	THC Non-Naïve (n = 38)	*P*
CNS	54	27	0.02
Lethargy or somnolence	32 (84)	10 (26)	<0.0001
Altered mental status	22 (58)	17 (45)	0.36
Musculoskeletal systems	32	20	0.093
Ataxia	16 (42)	13 (34)	0.64
Tremors, jitters, or tics	6 (16)	4 (11)	0.74
Hypotonia	5 (13)	2 (5)	0.43
Hypertonia	5 (13)	1 (3)	0.20
Circulatory and respiratory systems	21	18	0.74
Tachycardia	9 (24)	8 (21)	1.0
Bradycardia	0 (0)	3 (8)	0.24
Cardiac arrhythmia (not specified)	1 (3)	0 (0)	1.0
Chest pain	0 (0)	3 (8)	0.24
Respiratory insufficiency	5 (13)	1 (3)	0.20
Hypoxia	3 (8)	1 (3)	0.62
Hypotensive	3 (8)	2 (5)	1.0
Cognition, perception, emotional state, and behavior	7	21	0.01
Agitation or emotional outburst	7 (18)	9 (24)	0.78
Self-injurious behaviors	0 (0)	3 (8)	0.24
Anxiety	0 (0)	3 (8)	0.24
Aggression	0 (0)	3 (8)	0.24
Psychosis or psychotic episode	0 (0)	3 (8)	0.24
Skin and subcutaneous tissue	4	0	0.12
Pallor	4 (11)	0 (0)	0.12
Digestive system and abdomen	3	11	0.046
Nausea or vomiting	3 (8)	8 (21)	0.19
Abdominal pain	0 (0)	3 (8)	0.24
Speech and voice	0	4	0.12
Slurred speech	0 (0)	4 (11)	0.12
General signs and symptoms			
Fever	4 (11)	1 (3)	0.36
Seizure-like activity	2 (5)	1 (3)	1.0
Hypothermia	1 (3)	0 (0)	1.0
Headache	1 (3)	1 (3)	1.0
Blurred vision	1 (3)	0 (0)	1.0
Abnormal eye exam	11 (29)	5 (13)	0.16
Bloody stool	1 (3)	0 (0)	1.0
Decreased appetite	1 (3)	0 (0)	1.0
Increased appetite	0 (0)	1 (3)	1.0
Dehydration	8 (21)	3 (8)	0.19
Asymptomatic	2 (5)	6 (16)	0.26
Duration of clinical effects, mean (SD), h	19.3 (14.7)	5.0 (2.6)	<0.0001

Data are presented as number (percentage) unless otherwise indicated. Not all patients had symptoms, type of symptom, or duration of symptoms documented. Some patients had more than 1 symptom.

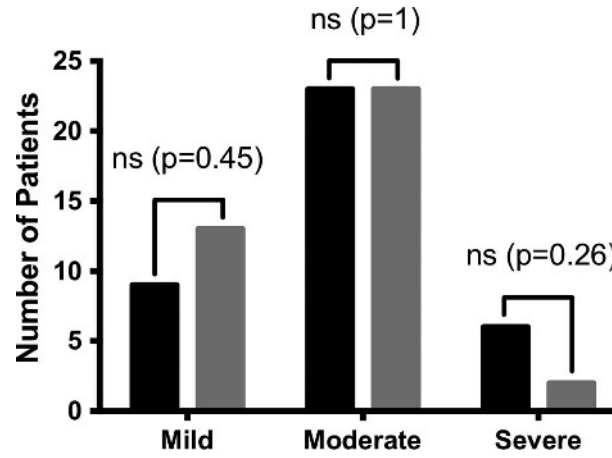

FIGURE 3. Comparison of clinical effects and subsequent medical intervention required in 76 children after acute marijuana (THC) intoxication. The THC-naïve patients (n = 38) are represented by the black bars and THC–non-naïve patients (n = 38) are represented by the gray bars. Mild effects were those perceived to be minimally bothersome and resolved rapidly, moderate effects required some form of medical treatment, and severe effects resulted in life-threatening symptoms and required intensive care treatment/support.

in the THC-naïve group compared with the THC–non-naïve group (0.73 [0.61] vs 0.19 [0.17]; $P < 0.0001$).

DISCUSSION

The present study provides unique observational evidence of excessive THC exposure in both naïve and non-naïve pediatric patients. The clinical consequences after THC exposure were different between these groups, with naïve patients exhibiting more central nervous system (CNS) effects and non-naïve patients exhibiting more cognitive, emotional, and gastrointestinal effects.

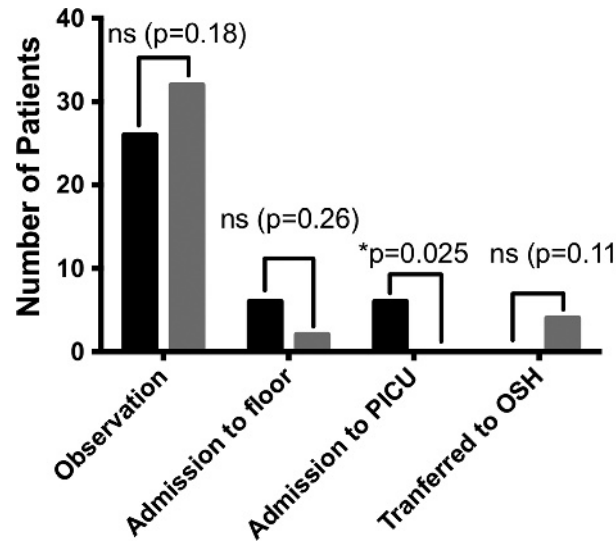

FIGURE 4. Summary of hospital disposition required in 76 children after acute marijuana (THC) intoxication. The THC-naïve patients (n = 38) are represented by the black bars and THC–non-naïve patients (n = 38) are represented by the gray bars. OSH indicates outside hospital.

Although this was a small study, there seems to be a direct relationship between the dose of oral THC ingested (mg/kg), hospital disposition, and level of medical intervention required in THC-naïve children.

It is well established that the clinical effects of THC depend on dose, route of administration, and tolerance of the user. These effects may be enhanced or altered by environmental factors as well as concomitant use of other substances such as ethanol and cocaine.[9] Previous reports have described the psychological and physiological effects of cannabis after intentional consumption and will not be further discussed in this study. Acute cannabinoid toxicity, however, has not been widely studied, especially in the era of high-potency THC products.[13,18]

This study corroborates symptoms previously reported after excessive THC exposure, yet highlights some important differences. Classic symptoms such as poor coordination and muscle strength, lethargy, sedation, difficulties concentrating, altered psychomotor activity, slurred speech, and slowed reaction times[6,9,11,17,19,22] were observed in both groups of our patients regardless of age or route of ingestion. Patients in the THC–non-naïve group, however, were more likely to experience cognitive, perceptual, and emotional symptoms (such as acute anxiety, positive psychotic symptoms) whereas patients in the THC-naïve group tended to experience lethargy/somnolence, respiratory insufficiency, tone abnormalities, and pallor. Children in the THC-naïve group also exhibited significantly longer THC-related effects compared with THC non-naïve patients. This may have been caused, in part, by the larger dose of THC consumed per kilogram of body weight as well as the type of THC exposure, specifically oral TCH from edible products. Of note, naïve patients experienced a 3-fold–longer time to admission after their estimated time of exposure, which may have allowed some abatement of THC-related effects.

Three patients in this study (all from the naïve group) were purportedly exposed to THC only through passive inhalation. Two of these children experienced moderate effects and 1 experienced major effects (data not shown). Although somewhat controversial, it has been stipulated that individuals exposed to THC through passive inhalation in unventilated environments can produce positive urine test results and experience drug effects.[22–24] Although adults may experience only mild effects, children (with their smaller size and higher minute ventilation) may experience more exaggerated effects.[25]

The inability to distinguish THC-containing edible products from innocuous non-THC oral products is a key factor behind the majority of hospital admissions and higher level of monitoring required in infants and young children exposed to THC.[17] Not surprisingly, the legalization of marijuana and subsequent growth in marijuana commercialization and availability in Colorado has resulted in a dramatic increase in the number of children presenting to Colorado's largest pediatric emergency department with THC-related admissions.[16] This upsurge in THC-related admissions has garnered attention at both the state and national level.[13,26] Other states that have decriminalized the possession of marijuana have also experienced an increase in unintentional exposures.[12] Although these reports are critical in describing trends and providing insight into the growing problem of unintentional THC exposure, they do not explore possible dose-response relationships or take into account the influence of tolerance among chronic users. Our data suggest that the response to THC-containing products in children is based on the dose and route of THC as well as previous exposure history. As the rate of THC-related intoxications increase, it will be important to accurately document the amount (mg/kg) of THC consumed so that the clinician may anticipate a patient's trajectory and clinical course.

There are limitations to this study that must be acknowledged. First, this was a relatively small study. Nevertheless, it is the largest study of its kind reported in pediatric patients. Second, although screened at study entry, unknown exposure to concurrent illicit/licit substances among study participants may have occurred. This could have influenced the type and severity of symptoms observed and reported. Third, the ability to accurately quantify the dose of THC consumed was challenging. The estimated amount of THC consumed was rarely reported or verifiable. This was especially true for secondhand inhaled exposures in naïve patients. Even when caregivers reported no edible THC products and admitted to smoking around the patients, we could not be certain if secondhand inhalation alone was responsible for the positive urine toxicology screen or if ingestion had also taken place. Fourth, a number of patient-specific variables may have influenced the findings and generalizability of the data. Specifically, the frequency of previous exposures (habituation), age of the patient, and other pharmacokinetic differences such as cytochrome p450 activity may impact drug metabolism and duration of THC effect. In addition, the variability of time elapsed between THC exposure and presentation to the hospital may have influenced the degree of symptom severity. Finally, because the non-naïve group was older and more verbal, they may have been able to express more cognitive and emotional symptoms. Despite these limitations, the current study provides important preliminary evidence on the relationship between the oral dose of THC ingested and clinical effects.

We anticipate that as additional reports of unintentional exposures and acute toxicities are published, important governmental policies will be implemented. In fact, since the legalization of marijuana in Colorado, we have already seen legislation to regulate the amount of marijuana concentrate that stores can sell, improved packaging of THC products (child-resistant packaging) and standardization of recreational edible serving sizes to 10 mg of THC, with a maximum of 10 total servings (100 mg of THC).[23,27] Most recently, there is legislation under consideration that requests a red stop sign printed on THC-containing labels and the word "candy" removed from edible products even if they are sweet, such as suckers or gummies. Furthermore, manufacturers would no longer be allowed to spray cannabis oil on premade edible items.[28]

CONCLUSIONS

Complete and accurate documentation of marijuana consumption (eg, mg/kg THC) in children after unintentional intoxication is rare. There seems, however, to be a direct relationship between estimated oral THC dose (mg/kg), hospital disposition, and level of medical intervention required. Clinical symptoms displayed, after THC exposure, are different between naïve and non-naïve children. Naïve children experience more CNS symptoms, longer duration of effects, and have longer hospital stays than non-naïve children. These findings should compel health care systems to develop standardized protocols and guidelines regarding the documentation of marijuana use and treatment algorithms to ensure appropriate care while minimizing harm and unnecessary treatments or procedures.

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