Brief Communication

Determination of contaminants in artisanal cannabis products used for childhood epilepsy in the Australian community: A sub-analysis of the ‘PELICAN’ study

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Abstract

Despite recent approval of pharmaceutical-grade cannabis products for the treatment of childhood epilepsy, some families continue to use artisanal cannabis products as a way to manage seizures in their children. However, such products are typically of unknown composition and quality, and may therefore pose an unpredictable health risk to the child. In the present analysis, 78 samples of cannabis products collected (as part of a previous study) from families of children with epilepsy (average age 8.8 ± 4.6 years) were analyzed for heavy metals (arsenic, cadmium, lead, and mercury), residual solvents (panel of 19 solvents) and pesticides (panel of 57 pesticides). Due to small sample volumes obtained, only a subset of samples was used in each analysis. Results showed that no cannabis sample exceeded the toxicity limits for heavy metals (n = 51 samples tested). Of the 58 cannabis samples tested for residual solvents, 17 (29%) contained concentrations of ethanol or isopropanol above the generally accepted limit of 5000 parts per million. With the volumes consumed, it was thought unlikely that children were consuming hazardous amounts of residual solvents, although this could not be ruled out in every case. Most samples (n = 31 samples tested) yielded inconclusive results for the pesticides, although one sample contained concentrations of bifenthrin that were 4.9 times higher than the acceptable limit. Overall, these results highlight the need for improved access to quality-assured cannabis products and the education of doctors, patients, and artisanal manufacturers around the contaminant exposure risk in unregulated cannabis products.

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1. Introduction

Epilepsy is a common neurological disorder affecting 0.5–1% of children [1]. Approximately one-third of people with epilepsy will experience treatment-resistance which is defined as failure of adequate trials of two tolerated, appropriately chosen antiepileptic drugs to achieve seizure-freedom [2]. Children unresponsive to conventional treatments face an increased risk of cognitive, behav-iorial, and psychosocial dysfunction that can have a negative impact on their health and development [3]. This prognosis has led to strong consumer interest in and uptake of alternative treatments such as artisanal ‘cannabidiol (CBD)-rich’ products as a way to manage seizures in children with epilepsy [4,5]. However, such products are typically of unknown quality, composition, and safety, and their use may conceivably pose unpredictable health risks to these children.

Despite increasing access to legal pharmaceutical-grade cannabis products globally, many consumers continue to use artisanal cannabis preparations. This may be done for various reasons including lower cost relative to the prescribed product, lack of awareness or knowledge of the patient access pathways, bias against pharmaceutical products, or perceived superior effectiveness and/or tolerability of artisanal products relative to the
prescribed products. Artisanal cannabis oils and tinctures are often concentrated to increase the concentrations of active ingredients such as CBD. This, in turn, may result in unusually high levels of residual contaminants in the final product [6], risking possible toxicity with oral ingestion. The lack of quality control poses potential health risks to individuals via exposure to cannabis contaminated with pesticides, heavy metals, and residual solvents. This would be of particular concern when consumed by children, or immunocompromised or seriously ill adults, and occurs on a long-term basis.

With many individuals continuing to self-medicate with artisanal cannabis preparations in Australia [4,5,7] and the US [8], contaminants may be unknowingly ingested by many vulnerable individuals suffering chronic illness, including children and adolescents with epilepsy. In a previous study, we collected individual samples of cannabis extracts from families in Australia who were using them to treat their child’s epilepsy, and conducted an analysis of cannabis samples from families across New South Wales and Queensland, Australia, from participants in the Paediatric Epilepsy Lambert Initiative Cannabinoid ANalysis (PELICAN) study. A total of 78 cannabis samples were collected from 41 families who were either currently using cannabis products to treat their child’s epilepsy (n = 34) or who had previously used such products and now stopped (n = 7). Of these, 37 families provided multiple samples. These included 68 liquid-based samples (oil or alcohol), six solid-based samples (four paste, one resin and one hash), three plant matter samples, and one crystal/powder-based sample. Aside from two families who had obtained a legal prescription, all other families were accessing unregulated artisanal cannabis preparations of unknown strength, composition, and quality.

2.1. Sample collection and storage

Samples (~2 mL) were collected between May 2016 and November 2017 across New South Wales and Queensland, Australia, from participants in the Paediatric Epilepsy Lambert Initiative Cannabinoid ANalysis (PELICAN) study. A total of 78 cannabis samples were collected from 41 families who were either currently using cannabis products to treat their child’s epilepsy (n = 34) or who had previously used such products and now stopped (n = 7). Of these, 37 families provided multiple samples. These included 68 liquid-based samples (oil or alcohol), six solid-based samples (four paste, one resin and one hash), three plant matter samples, and one crystal/powder-based sample. Aside from two families who had obtained a legal prescription, all other families were accessing unregulated artisanal cannabis preparations of unknown strength, composition, and quality. All other cannabis products are illegal and unregulated – here referred to as ‘artisanal products’ – which are generally of unknown composition and are typically sourced via the illegal gray or black market.

2. Methods

2.2. Sample preparation

The analysis, including detection, identification, and quantification, of four types of heavy metals, 19 types of residual solvents, and 76 types of pesticides (full list available in Supplemental Table S1) was performed by a National Association of Testing Authorities (NATA)-accredited analytical chemistry facility (ChemCentre, Perth, Western Australia). All samples were analyzed using quality-control standards using a 10% replicate approach except those with a small sample volume which were completed in duplicate as a minimum. To account for the variation in sample volumes remaining from prior analyses in the original protocol, a representative sampling approach was chosen. The maximum number of analyses possible on each sample was determined based on volume available, ensuring at least 30 samples per contaminant group. Samples containing >3 g were analyzed for all three categories of possible contaminants: 2.5–3 g for residual solvents and pesticides only; 2.0–2.5 g for pesticides only; 0.7–1.9 g for residual solvents and heavy metals only; 0.6 g for heavy metals only; and <0.5 g for residual solvents only. Using this approach, 51/78 samples were analyzed for heavy metals, 58/78 for residual solvents, and 31/78 for pesticides. Contaminant analysis methods are described in brief in the Supplemental Files.

2.3. Data interpretation

The list of heavy metals and their associated toxicological limits were obtained from the Australian Government Therapeutic Goods Order No. 93 Standard for Medicinal Cannabis for heavy metals [9]. The list of residual solvents and their associated toxicological limits were obtained from the International Council for Harmonisation guidelines for residual solvents [10]. Ethanol concentration was converted into alcohol by volume (ABV; % v/v) to provide an estimate of ethanol content using the density of ethanol (0.789 g/mL) and average density of the cannabis oil samples (0.819 g/mL). The average volume consumed by the child per day was calculated from original study data, with the typical serving administered either in ml (average 5.6 ml/day, range 0.5 – 16 ml/day) or drops (average 12.9 drops/day, range 2 – 40 drops/day). The list of pesticides and their associated toxicological limits were obtained from the European Pharmacopoeia 10th Edition [11] as per Australian government requirements. The Globally Harmonised System was used to categorize pesticides based on their toxicity ranging from ‘extremely hazardous’ to ‘unlikely to present acute hazard’ [12]. Limit of reporting was defined as the lower limit of quantification (LOQ), adjusted for volume for each individual sample. In cases where LLOQ exceeded the toxicity limit for a specific analyte, the data were deemed as inconclusive (‘unconfirmed safety’). In cases where LLOQ was less than the toxicity limit but not quantifiable, the specific analyte was deemed as ‘below safety limit’ (that is, the analyte was either below the toxicity limit or not detected). Samples where a specific contaminant was quantifiable and above the toxicity limit were deemed ‘above safety limit’. All plots were generated using GraphPad Prism 9 Software.
3. Results

Of the 51 cannabis samples tested for the heavy metals, concentrations of arsenic, cadmium, lead, and mercury were below the toxicity limit in 48/51 samples (94%) (see Fig. 1 and Supplementary Table S1). Results were inconclusive for 2/51 samples for arsenic, and one sample for cadmium and mercury each (see Methods for explanation). Of the 58 cannabis samples tested for residual solvents, 17/58 samples (29%) were above the limits specified for ethanol (>5000 ppm). All were liquid-based preparations. Estimated alcohol by volume (ABV) percentage for these samples was 6.68 ± 8.6% (v/v) on average (range, 0.61% – 25.10%). One 'paste'-like extract tested 1.2 times above the limit for isopropanol (>5000 ppm) with an estimated ABV of 0.63% v/v (see Fig. 2 and Supplemental Table S2). Results were inconclusive in 3/58 samples for 1,2-Dichloroethane, 6/58 samples for benzene, 1/58 for hexane, and one sample for methanol. One of the 31 samples tested for pesticides contained 4.9 times higher than the acceptable limit of bifenthrin (sample #44 in Supplemental Table S4). No other sample tested above the toxicity limit for any other pesticide. A large proportion of samples had inconclusive results for at least one pesticide: 21 samples had inconclusive results for 25/76 pesticides, four samples had inconclusive results for 35/76 pesticides, three samples for 26/76 pesticides, and one sample for 71/76 pesticides (see Supplementary Fig. S1-2 and Table S1-2).

4. Discussion

This current analysis of ‘artisanal’ cannabis samples administered to children with epilepsy in the Australian community found potentially unsafe levels of residual solvents, mainly ethanol, in approximately one quarter of the cannabis samples tested. In the manufacture of artisanal cannabis preparations, the incomplete evaporation of ethanol and other solvents prior to reconstitution with an oil-based diluent can lead to consumers ingesting higher amounts of residual solvents than anticipated, particularly if products are taken at high doses and/or for prolonged periods of time.

There are legitimate concerns around the potential harmful effects of ethanol on the developing brain, as well as the fact that alcohol consumption, particularly chronic and/or acute use of considerably large amounts of alcohol (e.g., “binge” drinking), and sudden alcohol withdrawal, can increase the risk of seizures [13]. Other alcohol-related factors for increased seizure risk include impaired sleep quality and interactions with antiepileptic drugs [14]. The effect of chronic low-level ethanol exposure on seizure frequency and neurodevelopment of children has not been systematically evaluated, with the current literature mostly focused on acute poisonings [15], fetal alcohol syndrome/effects [16] or extrapolated from preclinical studies. Children and adolescents exposed to serum ethanol concentrations of >0.125 mg/L may be asymptomatic or present with mild symptoms such as drowsiness, dizziness, and ataxia [17], while a serum ethanol concentration of 50-100 mg/dL (blood alcohol concentration or BAC of 0.05%) is considered a toxic dose in an infant or young child, with >100 mg/dL (>0.1 BAC) associated with central nervous system depression, vital sign abnormalities, and increased mortality in children [15].

Despite these concerns, ethanol is commonly used as a solvent in many oral liquid preparations for pediatric populations to improve drug solubility and/or as a diluent [18]. According to ICH guidelines, ethanol and isopropanol are ‘Class 3 solvents’ which are regarded as less toxic and of lower risk to human health. Such solvents may be administered in concentrations higher than the toxicity limit (5000 ppm) provided this is underpinned by good manufacturing practice or other quality-based requirements. In fact, the FDA-approved CBD-containing medication Epidiolex (known as Epidyolex in the UK and Australia), which is prescribed to treat rare childhood epilepsies, contains 79 mg/mL of ethanol, equivalent to 10% v/v anhydrous ethanol. With Epidiolex typically dosed at up to 10 mL/day (i.e., 20 mg/kg/day for a 50 kg individual), it can be deduced that relatively small amounts of ethanol are ingested by patients (~0.8 g) relative to a single USA standard drink which contains 14 g of ethanol.

The maximal amount of any extract consumed in the present study was 16 mL/day. As with the calculations for Epidiolex above, we conclude that in the ‘worst-case scenario’ presented in the current study, a child may have consumed 16 mL of a solution containing 25.1% ethanol, equivalent to 3 g/day of ethanol. The World Health Organization (WHO) states that ethanol content (as measured by %ABV) in over-the-counter medications should be less than 0.5% in children less than 6 years old, <5% for children 6–12 years old and less than 10% for children over 12 years [19]. Of the 17 samples that were above the toxicity limit, 12 were between 0.5 and 5%, two between 5 and 10%, and three exceeded 10%. The average age of the children and adolescents with epilepsy in our study was 8.8 ± 4.6 years [4] suggesting that some children were ingesting higher than appropriate levels of ethanol. However, it is reassuring that 71% of the samples tested contained less than 5% of ethanol content and this concentration is suitable for children aged 6–12 years according to WHO guidelines.

In addition to these high concentrations of residual solvents in some samples, one sample also tested above the safety limit for bifenthrin, an insecticide used in cannabis cultivation that can be toxic to human health if used inappropriately [20]. The exact implications of this observation are unclear, but it suggests that pesticide contamination is a legitimate concern which requires further investigation across a larger set of samples.

At the time the ‘PELICAN’ study was collecting samples from participants (pre-2017), legal pathways to accessing medicinal cannabis in Australia were still evolving and highly bureaucratic, time-consuming, and expensive for patients [7]. This represents a time in history when consumers had few alternatives to accessing medicinal cannabis and, artisanal ‘black market’ cannabis products, by comparison, were cheaper and easier to access. There are now better legal options available for accessing medicinal cannabis that avoid the concerns identified with unregulated products. In Aus-
tralia, Epidiolex is now a registered and government-subsidized medicine for the treatment of Dravet syndrome and Lennox-Gastaut syndrome [21] and an array of other CBD-containing products are available on prescription via schemes overseen by the Therapeutic Goods Administration [22]. Despite this, the use of artisanal cannabis products will undoubtedly continue because of the perception that artisanal products are more effective and/or better tolerated than pharmaceutical-grade cannabis products (typically pure CBD), and that the addition of Δ²-THC and minor cannabinoids may harness a supposed ‘entourage effect’ that enhances overall efficacy [23]. To-date, no randomized, controlled studies have compared pharmaceutical-grade CBD against artisanal cannabis preparations in a population with epilepsy, although preclinical studies are starting to shed light on the pharmacological interactions between cannabis constituents [24]. Meanwhile, in North America, concerns continue around an overall lack of mandatory testing of cannabis products to ensure patients are obtaining safe, quality-controlled product from licensed producers [6]. Several recent reports have described cannabis-derived products contaminated with microbes, heavy metals, pesticides, and other toxins [6].

The potential risk of contaminants in artisanal cannabis preparations, in addition to the variability in cannabinoid content and labeling accuracy [25,26], are legitimate concerns for consumer safety. Although the samples collected in the current study were intended for the treatment of seizures in children with epilepsy, it is possible that any individual seeking ‘CBD-rich’ artisanal products for treatment of a medical condition could be susceptible to purchasing contaminated products. The use of artisanal products accessed without prescription evades the necessary medical and regulatory oversight to ensure the patient’s suitability for medicinal cannabis (e.g., prior medication history to determine possible drug-drug interactions) and subsequent monitoring for safety and adverse events. Such products are unlikely to be optimized for safety or efficacy, indicating a need for improved patient access to safe, quality-controlled prescribed products from licensed manufacturers.

5. Limitations

Due to the sensitive nature of the use of artisanal cannabis products by families to treat their child’s epilepsy (i.e., an ‘invaluable’ and, in some cases, costly product that was in limited supply), only a small volume of the cannabis product was collected in the original study. Analysis of pesticides requires a higher sample volume for testing (i.e., >3 g) thereby limiting the number of samples that could be adequately tested in the present study. This resulted in a large proportion of samples producing inconclusive results across a range of pesticides. The sample size of the study was too small to conclusively determine overall safety and therefore the results should be interpreted with caution. Further, microbiological contamination (i.e., mycotoxins) was not tested in the present study. Finally, to maintain participant confidentiality, it was not possible to link the data collected on the cannabis sample in the original study (i.e., cannabinoid concentration, homemade versus purchased online etc.), precluding a more comprehensive assessment of possible factors contributing to contaminant exposure.

6. Conclusions

The results of the current analysis suggest that consumers and their families should not assume that artisanal cannabis preparations are inherently safe and should make an informed decision when considering using unregulated cannabis products for their children. There is a clear need for better and more streamlined pathways to quality-assured medicinal cannabis products of known composition at an affordable price and increased education of doctors, patients, and artisanal manufacturers on the risks of contaminants in artisanal cannabis preparations. Further, in places where cannabis is legal for personal use, provision of suitable standards for cultivation (e.g., list of approved pesticides) and/or greater capacity for self-testing of the end product is needed to optimize patient safety.
Declaration of Competing Interest

ISM is Academic Director of the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically-funded research program at the University of Sydney. He has served as an expert witness in various medicolegal cases involving cannabis and has received consulting fees from Medicinal Cannabis Industry Australia (MCIA) and Janssen. He currently acts as an advisor/consultant to Kinaxis Therapeutics, Psylo and Emyria. He reports research grants and salary support from the Australian National Health and Medical Research Council (NHMRC) and from Lambert Initiative for Cannabinoid Therapeutics. He is an inventor on patents WO2018107216A1 and WO2017004674A1, licensed to Kinaxis Therapeutics involving use of novel small molecules (non-cannabinoïd) to treat addictions and social deficits. ISM also has patents WO2020102857A1 and WO2021042178A1 related to use of small molecules (non-cannabinoïd) for treating weight gain and opioid withdrawal, as well as patents WO2019227167 and WO2019071302 issued, which relate to cannabinoïd therapeutics. AS has received consulting fees from the Medicinal Cannabis Industry Australia (MCIA). NL has been funded to serve on Advisory Boards for Chiesi, Mundipharma and Indivior, and has received research funding from Camurus for unrelated research. All other authors have no competing financial or non-financial interests to declare.

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Data availability

All data generated or analyzed during this study are included in this published article (and its Supplemental Files).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108496.

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