

Second-Hand Exposure of Staff Administering Vaporised Cannabinoid Products to Patients in a Hospital Setting

Nadia Solowij^{1,2}  · Peter Galettis^{2,3}  · Samantha J. Broyd¹  · Peter de Krey³ · Jennifer H. Martin^{2,3} 

© The Author(s) 2018. This article is an open access publication

Abstract

Background In many health settings, administration of medicinal cannabis poses significant implementation barriers including drug storage and safety for administering staff and surrounding patients. Different modes of administration also provide different yet potentially significant issues. One route that has become of clinical interest owing to the rapid onset of action and patient control of the inhaled amount (via breath timing and depth) is that of vaporisation of cannabinoid products. Although requiring a registered therapeutic device for administration, this is a relatively safe method of intrapulmonary administration that may be particularly useful for patients with difficulty swallowing, and for those in whom higher concentrations of cannabinoids are needed quickly. A particular concern expressed to researchers undertaking clinical trials in the hospital is that other patients, nurses, and clinical or research staff may be exposed to second-hand vapours in the course of administering vaporised products to patients. **Objective** The objective of this study was to take samples from two research staff involved in administering vaporised Δ^9 -tetrahydrocannabinol to participants in a clinical trial, to examine and quantitate cannabinoid presence.

Methods Blood samples from two research staff were taken during the exposure period for three participants (cannabis users) over the course of approximately 2.5 h and analysed using tandem mass spectrometry.

Results Blood samples taken over a vaporised period revealed exposure below the limit of detection for Δ^9 -tetrahydrocannabinol and two metabolites, using tandem mass spectrometry analytical methods.

Conclusions These results are reassuring for hospital and clinical trial practices with staff administering vaporised cannabinoid products, and helpful to ethics committees wishing to quantify risk.

Key Point

Staff administering vaporised cannabinoid products in a clinical setting do not appear to be at risk from second-hand exposure.

✉ Nadia Solowij
nadia@uow.edu.au

¹ School of Psychology, University of Wollongong, Wollongong, NSW 2522, Australia

² The Australian Centre for Cannabinoid Clinical and Research Excellence, New Lambton Heights, NSW, Australia

³ Discipline of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia

1 Introduction

Medicinal cannabis use, whilst now legal in many jurisdictions, remains a topic of great controversy. For its consideration for use in mainstream medical treatment pathways as a ‘therapeutic good’, or in clinical trials in hospital settings, it is crucial to understand the acceptability and side effects of the route of administration for different products and dosing regimens. One route that has become of clinical interest is that of vaporisation of

cannabinoid products. Although requiring a registered therapeutic device for administration, this is a relatively safe method of intrapulmonary administration that avoids risks associated with smoking and the formation of pyrolytic toxic compounds as it does not involve combustion [1]. It is also less likely to be associated with the cultural and societal assumptions linked with recreational cannabis use. The vaporisation route of administration may be particularly useful for patients with difficulty swallowing and for those in whom higher concentrations of cannabinoids are needed quickly. Peak plasma Δ^9 -tetrahydrocannabinol (THC) concentrations are reached within minutes of inhalation and have a rapid distribution phase [2–4].

The concern that other patients, nurses, and clinical or research staff may be exposed to second-hand vapours in the course of administering vaporised products to patients may limit the uptake of this form of treatment. Similar concerns have been raised for other medications, such as potential antimicrobial resistance development from exposure to nebulised antibiotics [5]. Previous well-controlled studies have determined that second-hand exposure to cannabis smoke may produce positive blood and urine test results and minor drug effects in non-smokers only under extreme conditions: non-smokers being in very close proximity to smokers using medium-high potency cannabis ad libitum in a small unventilated area for 1 h and using sensitive urinary assays with low cut-off criteria [6, 7]. Under extreme exposure conditions to inhaled cannabis smoke within a motor vehicle, no THC was detected in the oral fluid of those passively exposed [8], noting limitations with the interpretation of salivary cannabinoid assays in detecting the time of use and overall exposure, reviewed in [9]. No studies have investigated systemic exposure from second-hand vaporised cannabinoid product use. We used opportunistic sampling from staff administering vaporised pure THC within a clinical trial in a hospital setting to examine the likely risk.

2 Methods

In a clinical trial involving a vaporised ethanolic solution of 6 mg of THC [ISRCTN24109245] [10] using the Volcano[®] ‘Digit’ model vaporiser (Storz & Bickel GmbH & Co., Tuttlingen, Germany) set at 230 °C, two female clinical research staff gave informed consent to contribute blood samples to ascertain their exposure. Vaporisation of THC into the balloon and administration of the balloon filled with vapours for inhalation by trial participants (cannabis users and nonusers) was conducted in a small standard clinical assessment room on a hospital ward, away from other patients and near to imaging facilities. The approximate size of the room was 3 m × 2 m. One of the

staff (A; whose BMI was 20.1) administered the balloon to the participant and remained approximately 1 m away from the participant during inhalation and exhalation. The other staff member (B; BMI 20.2) was positioned inside the room but closer to the partially opened door, approximately 2 m away from the participant. There was no specific ventilation in the room aside from a standard small air conditioning vent. Participants inhaled and exhaled on average six to ten times to empty a balloon, and two balloons were administered. The first contained vaporised THC, the second contained the placebo (ethanol flavoured air; see [10] for methodology) and participants took on average 9 min to complete inhalation of both balloons (~ 5–6 min for the THC balloon and 3–4 min for the placebo balloon). Four blood samples were collected from staff over the course of approximately 2.5 h. The first was taken prior to any drug administration. The subsequent three were taken 5 min after each of the three participants completed inhalation of the balloons, with participants spaced approximately 1 h apart. Administration to the three participants occurred in the same room following the same procedures. As such, there was the possibility of cumulative exposure over the course of this approximate 2.5 h period.

Staff gave 5 mL of blood, collected into EDTA tubes, which were covered with aluminium foil to prevent light exposure and kept on ice until the end of the day when they were centrifuged at 2000×*g* for 10 min at 4 °C and the plasma extracted. Plasma samples were stored frozen at –80 °C and subsequently defrosted for assay by tandem mass spectrometry [11]. Plasma (50 µL) samples were combined with 100 µL of acetonitrile containing deuterated internal standards. Samples were then vortexed before being centrifuged at 15,000×*g* for 5 min. The supernatant was transferred into vials for measurement using liquid chromatography tandem mass spectrometry. The instrument was composed of a Shimadzu Nexera X2 ultra-high performance liquid chromatograph (Shimadzu Corporation, Kyoto, Japan) with a SCIEX 6500QTrap, a Kinetex Biphenyl column using a gradient of acetonitrile and 0.1% formic acid. The limit of quantitation was 0.5 ng/mL for each THC, and the metabolites 11-hydroxy- Δ^9 -tetrahydrocannabinol (OH-THC) and 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (COOH-THC). The limit of detection was 0.2 ng/mL for THC, 0.15 ng/mL for OH-THC and 0.25 ng/mL for COOH-THC.

One of the research staff (B) also performed a urinary drug test several hours after these procedures (ProScreen[™] Dip Test (US Diagnostics Inc, Huntsville, AL, USA); cut-off 50 ng/mL). Both staff also performed salivary tests for THC (Oratect[®] IIB (Alere[™] Toxicology Services, Portsmouth, VA, USA); cut-off 40 ng/mL).

3 Results

No cannabinoids were detected in plasma from either staff member (A or B) at baseline, nor, as shown in Table 1, at any of the three timepoints taken 5 min after completion of inhalation of THC vapours by each of three participants spaced 1 h apart. The urinary drug test was negative for cannabinoids. The salivary THC tests were both negative.

That the experiment and assays were valid, is evidenced by the quantification of THC and metabolites in the plasma of two of the THC-exposed male research participants (X and Y) shown in Table 2 (blood was not successfully drawn from the third participant because of unviable veins). Plasma concentrations in Table 2 correspond to baseline (pre-drug administration; 1), 5 min after inhalation of the two balloons (2) and 1 h later (3). Participant Y was a heavy cannabis user, explaining cannabinoid concentrations present at baseline.

4 Conclusions

These results suggest that there is little risk of second-hand exposure to clinical or research staff from administering vaporised THC within a clinical setting. Previous research has suggested that 35% of THC vapours inhaled are exhaled directly after inhalation [1] and we previously showed that 80% of the THC loaded into the vaporiser is delivered into the balloon [10]. Overall, this efficiency of delivery method is comparable to that achieved through a smoking route of cannabis administration [1]. These conditions and the conditions within which this small study was performed emulate administration of medicinal cannabis on a hospital ward, without the smoke, and optimised

Table 1 Results of liquid chromatography tandem mass spectrometry analysis of Δ^9 -tetrahydrocannabinol (THC) and metabolites (ng/mL) in plasma from two staff (A and B) exposed three times to exhaled vapours over the course of a 2.5 h period. Samples (1), (2) and (3) drawn 5 min after each of three participants spaced ~ 1 h apart were exposed to vaporised THC

Sample	THC	OH-THC	COOH-THC
A (1)	<LOD	<LOD	<LOD
A (2)	<LOD	<LOD	<LOD
A (3)	<LOD	<LOD	<LOD
B (1)	<LOD	<LOD	<LOD
B (2)	<LOD	<LOD	<LOD
B (3)	<LOD	<LOD	<LOD

COOH-THC 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol, *LOD* limit of detection, *OH-THC* 11-hydroxy- Δ^9 -tetrahydrocannabinol

Table 2 Results of liquid chromatography tandem mass spectrometry analysis of Δ^9 -tetrahydrocannabinol (THC) and metabolites (ng/mL) in plasma from two cannabis users (X and Y) exposed to vaporised THC. Samples drawn prior to THC administration (1); 5 min after THC administration (2); and 1 h later (3)

Sample	THC	OH-THC	COOH-THC
X (1)	<LOD	<LOD	<LOD
X (2)	183.4	1.6	<LOD
X (3)	15.2	1.0	4.9
Y (1)	12.9	3.4	75.6
Y (2)	223.5	4.5	66.1
Y (3)	28.9	6.3	68.3

COOH-THC 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol, *LOD* limit of detection, *OH-THC* 11-hydroxy- Δ^9 -tetrahydrocannabinol

the opportunity to detect cannabinoids in the biological fluids of staff, yet none were detected. Together with the fact that newer vaporisers, e.g. MiniVap (Hermes Medical Engineering, San Sebastián, Spain) have less ‘gas escape’ than the one used in this study, these outcomes should reassure researchers of the safety for staff in administering medicinal cannabis to patients in this setting. Nevertheless, the THC dose used in this study was relatively low (6 mg), and while higher doses are also not expected to result in detectable cannabinoids in clinical staff exposed under these conditions, replication of these findings with a larger sample size, more timepoints, alternate vaporisers, and with vaporisation of cannabis plant matter is warranted.

Acknowledgements The authors thank Sarah Gallagher, Elke Macdonald and Gabrielle Puckett for assistance with blood sampling, and Prof. Dion Forstner, Prof. Gary Liney and Robba Rai for access to facilities for the conduct of the study at the Cancer Therapy Centre, Liverpool Hospital facilitated by the Ingham Institute, Liverpool, NSW, Australia.

Compliance with Ethical Standards

Funding The original study that enabled the analyses reported here was funded by the National Health and Medical Research Council of Australia (APP1007593). Nadia Solowij was supported by an Australian Research Council Future Fellowship (FT1101007752).

Conflict of interest Nadia Solowij, Peter Galettis, Samantha J. Broyd, Peter de Krey and Jennifer H. Martin have no conflicts of interest directly relevant to the content of this article.

Ethics approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano[®]) for the pulmonary delivery of tetrahydrocannabinol. *J Pharm Sci.* 2006;95:1308–17.
2. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther.* 2007;82:572–8.
3. Zuurman L, Roy C, Schoemaker RC, Hazekamp A, den Hartigh J, Bender JCME, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol.* 2008;22:707–16.
4. Hartman R, Brown T, Milavetz G, Spurgin A, Gorelick D, Gaffney G, et al. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. *Clin Chem.* 2015;61:850–69.
5. Quom BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. *Ann Am Thorac Soc.* 2014;11:425–34.
6. Cone EJ, Bigelow GE, Herrmann ES, Mitchell JM, LoDico C, Flegel R, Vandrey R. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. *J Anal Toxicol.* 2015;39:1–12.
7. Herrmann ES, Cone EJ, Mitchell JM, Bidelow GE, LoDico C, Flegel R, Vandrey R. Non-smoker exposure to secondhand cannabis smoke. II. Effect of room ventilation on the physiological, subjective, and behavioral/cognitive effects. *Drug Alcohol Depend.* 2015;151:194–202.
8. Niedbala RS, Kardos KW, Fritch DF, Kunsman KP, Blum KA, Newland GA, Waga J, Kurtz L, Brinsgeest M, Cone EJ. Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. *J Anal Toxicol.* 2005;29:607–15.
9. Drummer O. Drug testing in oral fluid. *Clin Biochem Rev.* 2006;27:147–59.
10. Solowij N, Broyd SJ, van Hell HH, Hazekamp A. A protocol for the delivery of cannabidiol (CBD) and combined CBD and Δ^9 -tetrahydrocannabinol (THC) by vaporisation. *BMC Pharmacol Toxicol.* 2014;15:58.
11. Galettis P. Development of a simple LCMSMS method for THC and metabolites in plasma. *Asia Pac J Clin Oncol.* 2016;12(S6):S24.