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

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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 D9-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 D9-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.

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Original Research: Short Communication

Secondhand exposure of staff administering vaporised cannabinoid product to patients in a hospital setting

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Running head: Secondhand exposure to vaporised Δ^9-tetrahydrocannabinol

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Abstract

Background In many health settings, administration of medicinal cannabis use 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 due to rapid onset of action and patient control of 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 which 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, clinical or research staff may be exposed to secondhand vapours in the course of administering vaporised products to patients. We elected 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 hours and analysed using tandem mass spectroscopy.

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 spectroscopy analytical methods.

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

Key findings: Staff administering vaporised cannabinoid products in a clinical setting do not appear to be at risk from secondhand exposure.

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, clinical or research staff may be exposed to secondhand 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 secondhand 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 one hour and using sensitive urinary assays with low cutoff 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 time of use and overall exposure, reviewed in [9]. No studies have investigated systemic exposure from secondhand 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 6mg 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 3m x 2m. One of the staff (A) administered the balloon to the participant and remained approximately 1m away from the participant during inhalation and exhalation. The other staff member (B) was positioned inside the room but closer to the partially opened door, approximately 2m 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 6-10 times to empty a balloon, and two balloons were administered. The first contained vaporised THC, the second placebo (ethanol flavoured air; see [10] for methodology) and participants took on average 9 minutes to complete inhalation of both balloons (~5-6 minutes for the THC balloon and 3-4 minutes for the placebo balloon). Four blood samples were collected from staff over the course of approximately 2.5 hours. The first was taken prior to any drug administration. The subsequent three were taken 5 minutes after each of three participants completed inhalation of the balloons, with participants spaced approximately one hour 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 hour 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 x 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 spectroscopy [11]. Plasma (50µl) samples were combined with 100µl of acetonitrile containing deuterated internal standards. Samples were then vortexed before been centrifuged at 15000xg for 5 mins. The supernatant was transferred into vials for measurement using liquid chromatography tandem mass spectrometry (LCMSMS). The instrument was composed of a Shimadzu Nexera2 UHPLC with an 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 (LOD) 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^{TM} Dip Test; cutoff 50ng/ml). Both staff also performed salivary tests for THC (Oratect IIIB; cutoff 40ng/ml).

3 Results

No cannabinoids were detected in plasma from either staff member (A: BMI 20.1, or B: BMI 20.2) at baseline, nor, as shown in Table 1, at any of the three timepoints taken 5 minutes after completion of inhalation of THC vapours by each of three participants spaced one hour apart.

Table 1 Results of LCMSMS analysis of 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 hour period. Samples (1), (2) and (3) drawn 5 minutes after each of three participants spaced ~1 hour 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

LCMSMS: liquid chromatography tandem mass spectrometry; THC: Δ^9-tetrahydrocannabinol; OH-THC: 11-hydroxy-Δ^9-tetrahydrocannabinol; COOH-THC: 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol

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 due to unviable veins). Plasma concentrations in Table 2

correspond to baseline (pre-drug administration; 1), 5 minutes after inhalation of the two balloons (2), and 1 hour later (3). Participant Y was a heavy cannabis user, explaining cannabinoid concentrations present at baseline.

Table 2 Results of LCMSMS analysis of 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 minutes after THC administration (2); and one hour 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

LCMSMS: liquid chromatography tandem mass spectrometry; THC: Δ^9-tetrahydrocannabinol; OH-THC: 11-hydroxy-Δ^9-tetrahydrocannabinol; COOH-THC: 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol

4 Conclusions

These results suggest that there is little risk of secondhand 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 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) 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 utilised in this study was relatively low (6mg), 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.

Compliance with Ethical Standards

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Conflicts of interest: All authors declare that they have no conflict of interest.

Ethical 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.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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