

Transfer of Inhaled Cannabis Into Human Breast Milk

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OBJECTIVE: To evaluate the transfer of delta-9-tetrahydrocannabinol and its metabolites into human breast milk after maternal inhalation of 0.1 g cannabis containing 23.18% delta-9-tetrahydrocannabinol.

METHODS: In this pilot pharmacokinetic study, breast milk samples were collected from mothers who regularly consumed cannabis, were 2–5 months postpartum, and exclusively breastfeeding their infants. Women were anonymously recruited for the study. After discontinuing cannabis for at least 24 hours, they were directed to obtain a baseline breast milk sample, then smoke a pre-weighed, analyzed, standardized strain of cannabis from one preselected dispensary, and collect breast milk samples at specific time points: 20 minutes and 1, 2, and 4 hours. Quantification of delta-9-tetrahydrocannabinol and its metabolites in these collected breast milk samples was performed by high-performance liquid chromatography tandem mass spectrometry.

RESULTS: A total of eight women were enrolled. Most were occasional cannabis smokers and one a chronic user. Delta-9-tetrahydrocannabinol was detected at low concentrations at all the time points beyond time zero. No metabolites were detected at any time point. Delta-9-tetrahydrocannabinol was transferred into mother's milk such that exclusively breastfeeding infants ingested an estimated mean of 2.5% of the maternal dose (the calculated relative infant dose=2.5%, range 0.4–8.7%).

The estimated daily infant dose was 8 micrograms per kilogram per day.

CONCLUSION: This study documents inhaled delta-9-tetrahydrocannabinol transfer into the mother's breast milk. Low concentrations of delta-9-tetrahydrocannabinol were detected. The long-term neurobehavioral effect of exposure to delta-9-tetrahydrocannabinol on the developing brain is unclear. Mothers should be cautious using cannabis during pregnancy and breastfeeding.

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Legalization of recreational cannabis use in several states has caused growing unease in the medical community regarding the health risks associated with this drug, especially in pregnant and breastfeeding women. Although cannabis is one of the most widely used phytocannabinoid drugs in the world, understanding of the long-term neurobehavioral effect of cannabis use, particularly in the developing brain, is limited to observational and animal data.^{1–7}

Cannabis sativa is most commonly smoked, inhaled, or ingested orally. Cannabis smoke contains more than 150 known compounds.⁸ Delta-9-tetrahydrocannabinol, the most psychoactive of the phytocannabinoids, is highly lipophilic and is stored in adipose tissues for long periods, varying from weeks to months. Once inhaled, delta-9-tetrahydrocannabinol enters the plasma compartment almost instantly from the pulmonary tree and then redistributes to highly vascularized tissues (brain, liver, and other tissues). Thus, plasma concentrations are rather brief (minutes) and central nervous system concentrations slightly longer (2 hours). Remaining concentrations in the plasma are rapidly metabolized in the liver. Although the elimination life is 20–36 hours, in chronic users, it might be as long as 4 days.

Small-to-moderate secretion of tetrahydrocannabinol into breast milk has been reported; however,

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these reports may not adequately represent concentrations of tetrahydrocannabinol found in breast milk today with newer commercialized cannabis products.⁹ The objective of this pilot pharmacokinetic study was to evaluate the transfer of delta-9-tetrahydrocannabinol and its metabolites into human breast milk at 20 minutes and at 1, 2, and 4 hours after maternal inhalation of 0.1 g cannabis containing 23.18% of delta-9-tetrahydrocannabinol. This dose was chosen after extensively reviewing older studies wherein an average cannabis cigarette contained approximately 0.6 g of cannabis, containing approximately 3.55% tetrahydrocannabinol. This dose would amount to approximately 21.3 mg of tetrahydrocannabinol.

MATERIALS AND METHODS

We designed this pharmacokinetic study to measure the transfer of inhaled cannabis into human breast milk. Institutional review board approval for this study was obtained from Texas Tech University Health Sciences Center (A16-3968). The participants were recruited through the InfantRisk website, flyers posted in Colorado community lactation social media sites, and word of mouth through community-based breastfeeding groups. Participants were required to be 18–45 years of age, exclusively breastfeeding, 1–6 months postpartum, smoking cannabis while breastfeeding, and to have delivered at 37 weeks of gestation or more. Participants selected were from Denver, Colorado area and were willing to purchase the flower of a specific cannabis strain from a preselected Denver dispensary. Exclusion criteria included ingestion of cannabis orally, other drugs of abuse, and other medications or herbal products. Pregnant patients and women supplementing their infants with formula or solids were also excluded from this study. The study was open from January 2017 until October 2017.

Participants' breast milk samples were collected in polypropylene vials, which were previously determined to not bind tetrahydrocannabinol. Before initiating the study, we tested these vials by assessing stability of delta-9-tetrahydrocannabinol by spiking blank milk standards with known concentrations at different storage conditions. Thereafter the extraction efficiency along with estimated concentrations was determined with no concentration changes observed, which demonstrated that these collection vials were appropriate for breast milk collection. To ensure complete anonymity, we waived documentation of signed consent. Each participant received a complete copy of the consent along with a sheet reviewing frequently asked questions, written explanation about the

research activity, complete explanation that participation was voluntary, and acknowledgment that submitting samples implied consent. Each participant also received a toll-free phone number and was instructed to call if she desired to review the instructions, consent process, or any other questions arising concerning the study.

Once a participant indicated interest in the project, she was instructed to obtain a breast milk collection kit, which were made available for anonymous pickup at a local community center and included a new glass pipe, six polypropylene bottles for breast milk collection, freezer packs, a shipping container, a shipping label void of any identifying patient information, and complete instructions on how to proceed with the study protocol. A questionnaire was included, which asked about the consumption of cannabis such as frequency, amount, and preferred method, and also about any other drug use. Information about infant age and mothers' body weight at the time of study was also collected. Participants were asked to purchase a preweighed sample of Presidential Kush cannabis (0.1 g with delta-9-tetrahydrocannabinol content=23.18%) at a single specified dispensary to standardize the dose and concentration of the product being studied. They were instructed to abstain from all cannabis consumption for 24 hours before the commencement of the study. Milk samples collected just before smoking were considered the "zero hour" sample. Participants were then to place 0.1 g of cannabis into the bowl of the provided glass pipe, light, and inhale until consumed (equivalent to approximately three to four hits over approximately 10–20 minutes). We also advised the presence of an assistant to ensure quality of sampling. Using the beginning of consumption as the start time, breast milk samples were then collected at 20 minutes and 1, 2, and 4 hours after inhalation.

Mothers were advised to pump their breasts with an electric pump, mix right and left breast milk samples, and decant 1–2 ounces into the proper sample bottle. Samples were immediately stored in the freezer after each collection. On average, 2 ounces of breast milk were collected, frozen, and mailed to our facility overnight. No compensation was given to study participants. The participants collected only one set of samples. Because this study did not require comparison between groups, it did not require a null hypothesis or mean comparisons. We were simply quantifying the drug concentrations in the collected breast milk samples over time. Thereby each time interval was grouped into mean \pm standard error and the area under the curve was used to estimate the



average dose and the relative infant dose, which is the percentage of the mother's dose that the infant might receive daily from exposure to this drug in its mother's breast milk when breastfeeding exclusively.

Delta-9-tetrahydrocannabinol concentrations in the breast milk samples were measured using high performance liquid chromatography mass spectrometry. Milk samples were thawed and 0.1 mL was transferred to acetonitrile for protein precipitation. Internal standards (final concentration 50 ng/mL) were added to each sample and standards. The analyte and internal standards were analyzed by AB Sciex QTRAP 5500 ultrahigh-performance liquid chromatography tandem mass spectrometry and attained by tandem mass spectrometry detection in positive ion mode. Data were acquired by multiple reaction-monitoring modes with mass transitions as follows: m/z 315– m/z 193.2 for delta-9-tetrahydrocannabinol and similarly for internal standard m/z 395.1– m/z 213 was performed. Chromatographic separation was achieved on Agilent Poroshell column (4.6×50 mm 2.7 microns) and a thermostatic column compartment (40°C). The concentration of each analyte was determined from the ratio of the peak area of the drug to the peak area of its internal standard and comparison of this ratio with the calibration curve that was generated from the analysis of blank human breast milk with known concentrations of delta-9-tetrahydrocannabinol. The range for the curve constructed was 1.9–500 ng/mL with a correlation coefficient of 0.99 (Fig. 1). The recoveries of analyte and internal standard from human breast milk were determined by comparing the peak areas of the analyte in spiked human breast milk samples with those of analyte spiked into the post extracted breast milk blank by adding equivalent concentrations of the analyte. Percent recovery was calculated to be 88%. Tetrahydrocannabinol metabolites 11-OH-delta-9-tetrahydrocannabinol and 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol were also determined using mass spectrometry. Chromatographic conditions were similar to delta-9-tetrahydrocannabinol with mass transitions as m/z 331.1– m/z 313.3 for 11-OH-delta-9-tetrahydrocannabinol and m/z 345.1– m/z 193.3 for 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol. Our goal was to recruit 50 study volunteers, but we were unable to recruit this number.

RESULTS

A total of eight women participated in the study. Four of the participants indicated they used cannabis infrequently and one used cannabis seven to 10 times during the prior week. The preferred method of consumption was smoking and the reported range of

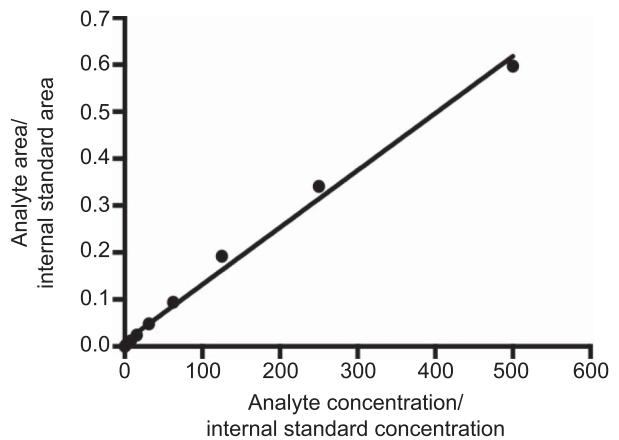


Fig. 1. Linear calibration curve with correlation coefficient, $r^2=0.99$. Each data point represents the average of triplicate.

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cannabis use was from 0.025 to 1 g per day. Three study participants chose not to return the questionnaire (Table 1). The participants reported consumption of no other medications during the time of the study other than multivitamins and probiotic supplements. The median postpartum interval was 5 months and ranged from 3 to 5 months.

Dosage administered to each mother was calculated based on the reported delta-9-tetrahydrocannabinol content of this cannabis product in 0.1 g of cannabis. The analytical report for Presidential Kush cannabis documented a delta-9-tetrahydrocannabinol content of 23.18% or 23.18 mg per 0.1 g administered. The average concentration of delta-9-tetrahydrocannabinol in breast milk was 53.5 ng/mL. The mean maximum concentration in breast milk observed was 94 ng/mL, which occurred at 1 hour after the consumption of the cannabis. The daily absolute infant dose was estimated as average consumption multiplied by an average breast milk intake of 150 mL/kg per day.^{10,11} Based on these data, the estimated relative infant dose was calculated at 2.5%, and the average absolute infant dose was estimated at 8 micrograms per kilogram per day (Table 2). Area under the breast milk concentration time curve from zero to the time of the last sample was estimated by the linear trapezoidal rule. All these calculations were done using Graphpad Prism 6. Figure 2 depicts the mean±SD concentrations of delta-9-tetrahydrocannabinol in the breast milk.

The results at zero hour were exceedingly low in six of eight participants (less than 2 ng/mL), suggesting that most participants were able to abstain



Table 1. Prestudy Self-Reported Cannabis Smoking

Patient No.	Postpartum (Mo)	Cannabis Use/Wk (No. of Times)	Daily Cannabis Use (g)	Method of Consumption
1	5	1	0.25	Inhalation
2		ND		
3	3	7–10	0.5–1	Inhalation
4	5	3–5	0.05	Inhalation
5	5	5	0.05	Inhalation
6		ND		
7	3	1–3	0.025	Inhalation
8		ND		

ND, not disclosed.

from using cannabis for 24 hours before the collection of the samples. A relatively low but measurable concentration of delta-9-tetrahydrocannabinol (5.8 and 15.8 ng/mL) was found at zero time in two of the participants, which suggests some residual accumulations of delta-9-tetrahydrocannabinol either from prior heavy use or use close to the start of breast milk collection. Data obtained for five of eight individuals are shown in Table 3 and graphed in Figure 3.

Neither 11-OH delta-9-tetrahydrocannabinol nor 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol, metabolites of delta-9-tetrahydrocannabinol, was quantifiable in these samples because their concentrations were below our limit of detection (0.097–3.15 ng/mL).

DISCUSSION

Our findings demonstrate breast milk concentrations of delta-9-tetrahydrocannabinol peaked at 1 hour, with a peak of 94 ng/mL (range 12.2–420.3 ng/mL), and receded slowly over the subsequent 4 hours. Delta-9-tetrahydrocannabinol was transferred into mother's milk such that an exclusively breastfeeding infant ingests an estimated 2.5% of the maternal dose (range 0.4–8.7%). Although the transfer of delta-9-tetrahydrocannabinol into the plasma compartment is almost instantaneous, the transfer of delta-9-tetrahydrocannabinol into breast milk in our study appears to be slightly slower than the transfer into the plasma compartment.

Numerous other studies with similar doses in cigarette formulations suggest that plasma concentrations in humans range as high as 94.3, 107.4, and 155.1 ng/mL after smoking single cigarettes of 1.32%, 1.97%, or 2.54% tetrahydrocannabinol, respectively.¹² Other studies reported plasma concentrations ranging from 45.6 and 187.8 ng/mL and 76–267 ng/mL after smoking of a single cigarette.^{13,14} It is believed rapid volatilization of delta-9-tetrahydrocannabinol leads to plasma concentrations rising even before the end of the smoking session.¹⁵ It is well established in breast-

feeding medicine that drugs with high volumes of distribution such as cannabis or propofol rapidly reach clinically significant concentrations in the plasma and central nervous system, but thereafter dissipate rapidly as a result of redistribution into peripheral compartments such as skeletal muscle or adipose tissue. This invariably reduces the concentrations found in breast milk.

We analyzed all samples for tetrahydrocannabinol metabolites 11-OH-delta-9-tetrahydrocannabinol and 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol. These two metabolites were not detectable (with lower limits of detection at 0.097 ng/mL) for two possible reasons. One, the participants were instructed to stop using cannabis for 24 hours before the study; thus, metabolites had dissipated. Two, our breast milk samples were collected long before plasma concentrations of metabolites became evident. Thus, we did not find measureable concentrations of metabolites in breast milk within the 4 hours of this study. In addition, metabolites of delta-9-tetrahydrocannabinol

Table 2. Pharmacokinetic Parameters of Delta-9-Tetrahydrocannabinol in Human Breast Milk Samples (N=8)

Parameter (Units)	Calculated Value*	Median (Range)
AUC (ng/h/mL)	213.9	110.5 (33.9–744.4)
C _{avg} (ng/mL)	53.5	27.6 (8.4–186.1)
C _{max} (ng/mL)	94	44.7 (12.2–420.3)
T _{max} (h)	1	1 (1–2)
Infant dose (micrograms/kg/d)	8	4.1 (1.3–27.9)
RID (%)	2.5	1.3 (0.4–8.7)

AUC, area under the drug concentration time curve; C_{avg}, average drug concentration across the dose interval; C_{max}, maximum drug concentration across the dose interval; T_{max}, time at which maximum concentration is observed; RID, relative infant dose for delta-9-tetrahydrocannabinol in milk.

* Calculated value is obtained from the combined data at each time point for each parameter.



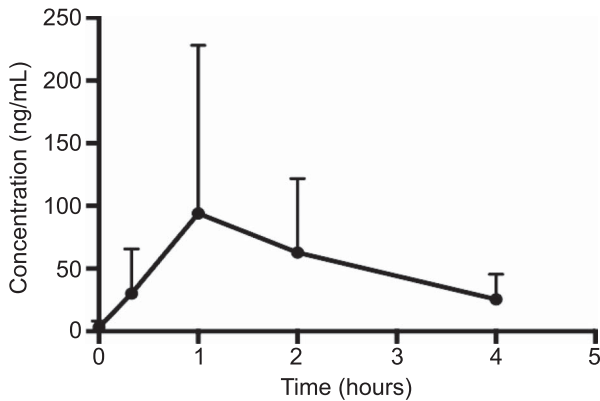


Fig. 2. Mean concentration time profile of delta-9-tetrahydrocannabinol in human breast milk (mean±SD, n=8). Baker. *Inhaled Cannabis in Human Breast Milk. Obstet Gynecol* 2018.

are known to be more water-soluble and more polar than the parent drug. These two properties may make it more difficult for metabolites to enter the breast milk compartment.

The strength of our study was our attempt to standardize the pharmacokinetic methodology for detection of delta-9-tetrahydrocannabinol in breast milk samples. It is clear that human breast milk is subject to change as a function of infant age, prematurity, and volume. In women, 1–6 months postpartum exclusively breastfeeding, regardless of weight or body habitus, the breast milk compartment along with drug entry and exit remains fairly consistent.¹⁶ In our study, a single cannabis dispensary was chosen that was willing to set aside a certain preweighed standardized product so that we could predetermine the

dose each mother received. Second, but more importantly, we had access to the analytics for the product selected, which accurately quantified the percentage of delta-9-tetrahydrocannabinol (23.18%).

Recruitment was challenging possibly as a result of the fact that women who use cannabis products and are pregnant or breastfeeding fear the legal ramifications of being reported. Second, we asked women of their own volition to seek out the breast milk sample kits and to purchase the preselected product. This task was perhaps too onerous for some women.

A significant limitation of this study was the lack of corresponding plasma samples for comparison, but at the same time, anonymity was necessary for the protection of the participants. Another weakness of this study was that we were not able to verify consumption or sample pumping at the allotted times. We did encourage participants to have a partner available to 1) assure their infants' welfare and 2) help the participant stay as close to the specified timeline as possible. We believe that similarity between the values obtained in the breast milk curve as well as that all eight participants peaked and cleared the delta-9-tetrahydrocannabinol in a period of 4 hours would suggest that most of participants did in fact abstain from cannabis use 24 hours before "zero time." However, there remain many unanswered questions: 1) What is the plasma level in the breastfeeding infant that is exposed to cannabis products through human breast milk? 2) What effect would repeated and continuous doses have on breast milk concentrations? 3) How much delta-9-tetrahydrocannabinol would transfer into a mother's breast milk after the use of oral cannabis products? 4) What do exogenous cannabis

Table 3. Drug Concentrations Observed Across the Dose Interval for Each Individual

	Sample ID							
	1	2	3	4	5	6	7	8
	Concentration (ng/mL)							
Time (h)								
0	ND	ND	ND	ND	5.8	15.8	ND	ND
0.33	7.0	11.1	16.3	12.3	47.1	115.8	8.2	23.4
1	11.3	34.8	47.2	5.9	115.8	420.2	19.3	97.3
2	17.3	42.2	28.5	12.2	95.2	193.3	27.8	83.5
4	9.2	21.7	10.7	4.7	67.2	43.0	24.2	24.4
AUC (ng/h/mL)	48.9	119.7	101.3	33.9	331.1	744.4	89.1	242.7
C _{avg} (ng/mL)	12.2	29.9	25.3	8.4	82.7	186.1	22.2	60.6
C _{max} (ng/mL)	17.6	42.1	47.2	12.2	115.8	420.3	29.8	97.3
RID (%)	0.6	1.4	1.2	0.4	3.8	8.7	1.0	2.8

ND, not determined (below the level of detection); AUC, area under the drug concentration time curve; C_{avg}, average drug concentration across the dose interval; C_{max}, maximum drug concentration across the dose interval; RID, relative infant dose for delta-9-tetrahydrocannabinol in milk.



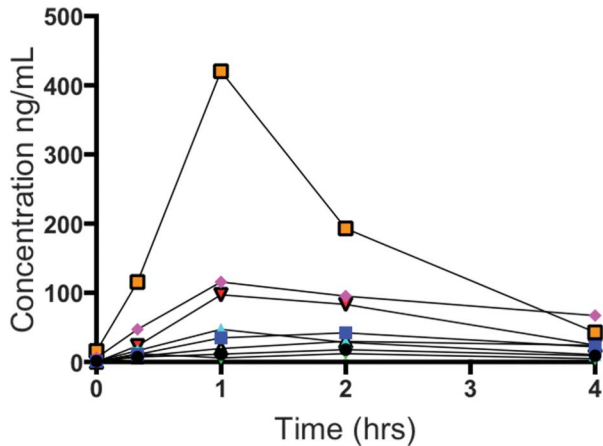


Fig. 3. Illustrated graph of each patient's data points (n=8). Each color represents an individual.

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products do to the endocannabinoid signaling system? Finally, the most clinically significant question: 5) What is the lasting effect of exposing developing infants to cannabis? It remains unclear what exposure to cannabis products during this critical neurobehavioral development period will mean for the infant. These questions will require an enormous effort to determine.

Thus, larger scale investigations are warranted and necessary to enable us to counsel women who may be using cannabis medicinally or recreationally.

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