Opioids, and Cannabis in Breastfeeding Mothers

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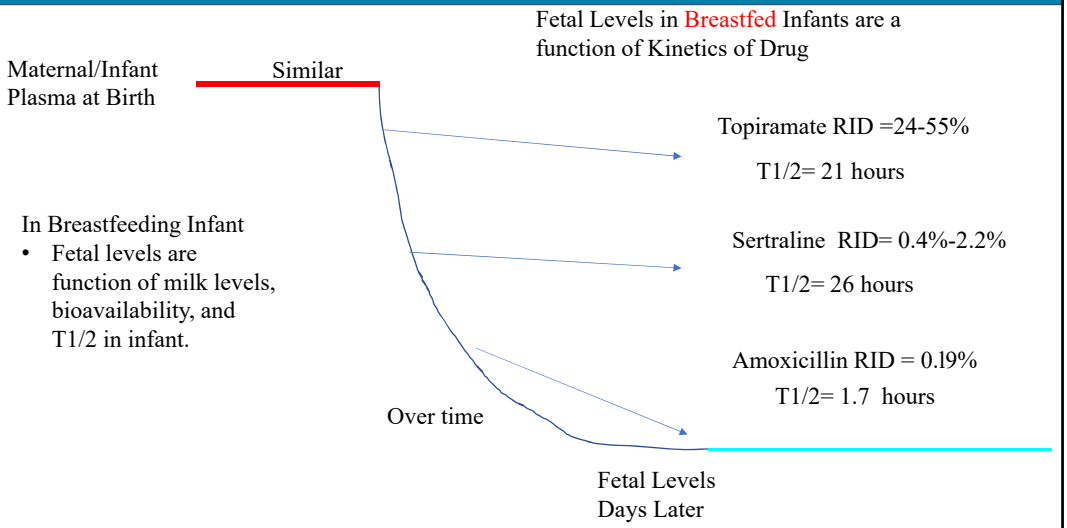
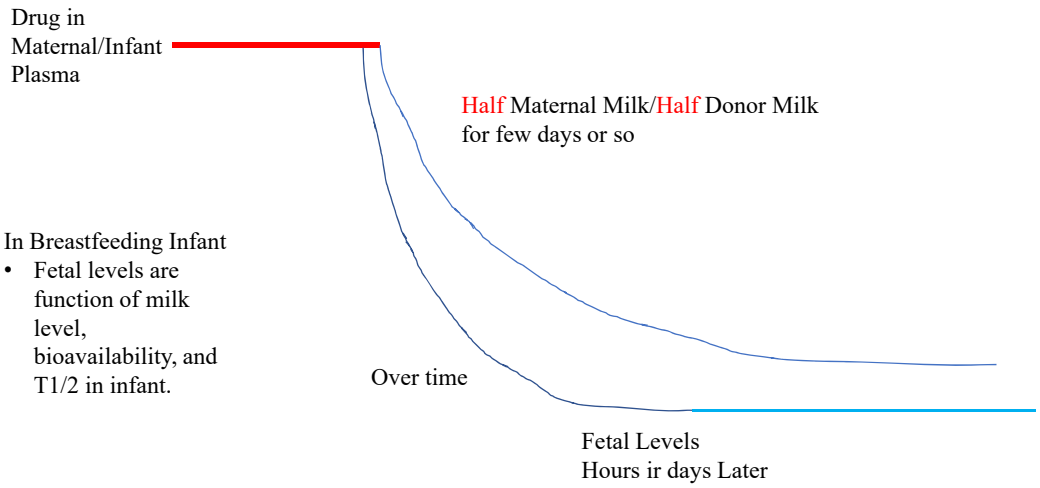
InfantRisk Center Method for Reducing Exposure in Infant



Hale Method for Reducing Drug Exposure in Infant



In Breastfeeding Infant

- Fetal levels are function of milk level, bioavailability, and T1/2 in infant.

Analgesics and Opiates

Morphine/Heroin & Breastfeeding

- Morphine Doses in Milk, Range all over
- In Adults (and probably infants), ORAL bioavailability < 30%
- Poor oral bioavailability (< 30% ??), due to sequestration in the infant's liver limits systemic levels in infant.
- Infants under 1 month of age have a prolonged elimination half-life and decreased clearance of morphine relative to older infants.
- Remember: Infants develop tolerance also. Thus moms who've exposed infant in utero, can probably safely breastfeed.
  - It even reduces withdrawal in infant.
- Unfortunately, DATA with morphine is really poor, so you must use morphine with great caution.
- At least 4 deaths have been reported(to me). At least 3 may be due to parental "administration" of direct doses to infant???

1. Feilberg VL, Rosenborg D, Broen Christensen C, et al. Excretion of morphine in human breast milk. Acta Anaesthesiol Scand. 1989;33:426–8.
2. Ito S. Opioids in breast milk: Pharmacokinetic principles and clinical implications. J Clin Pharmacol. 2018;58 Suppl 10:S151–S163.

Codeine

- Codeine metabolized to "morphine" the active ingredient.
- Use of codeine in breastfeeding moms Highly controversial following Koren paper in 2006 of a mother with rapid metabolism.[1]
  - Paper was recently retracted by journal after extensive controversy.
  - Questions surrounding this paper were: *how did the baby get that much codeine from milk?????.*
  - We don't think infant ingestion was due to "milk" intake ???
- As a case of unintended consequences, the Scheduling of Codeine dramatically INCREASED the number of acetaminophen/codeine 300/30 mg and 300/60 mg combination products prescribed by 597% and 1056%, respectively in the months after their rescheduling to CII.
  - The OB residents couldn't write for Hydrocodone, so they wrote for Codeine!

1. Koren, G., Cairns, J., Chitayat, D., Gaedigk, A. & Leeder, S.J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* **368**, 704 (2006).
2. Zipursky J, Juurlink DN. The Implausibility of Neonatal Opioid Toxicity from Breastfeeding. Clin Pharmacol Ther. 2020 Nov;108(5):964-970. doi: 10.1002/cpt.1882. Epub 2020 Jun 25. PMID: 32378749.

Methadone

- Opioid with long half-life
- Half-life = 13-55 hours
- Methadone is a potent and very long-acting opiate analgesic. It is primarily used to prevent withdrawal in opiate addiction.
- In 12 breastfeeding women on methadone maintenance doses ranging from 20-80 mg/day, the mean concentration of methadone in milk was 116 (72-160) µg/L respectively. This equates to a mean of 2.79% of the maternal dose per day.
- Excellent study of 8 women with doses of 40-105 mg/d
  - Relative infant dose = 2.8%
- Always ASK the DOSE !!!!!!

Methadone

- Approved by AAP for use in Breastfeeding mothers(2001)
- Higher doses such as 80-120 mg/day reduce the addicts' use of heroin by reducing the euphoria of heroin. Lower doses do not.
- At higher doses, caution is recommended. Observe for sedation.
- Withdrawal in newborn infants is slow and generally starts about 3-4 days.
  - Withdrawal can last weeks.
  - Symptoms include: hyperactivity, tremors, hypertonia, jitteriness.
- May be used to treat other OPIATE withdrawal.

Buprenorphine

- Buprenorphine (Belbuca, Probuphine, Buprenex)
  - Buprenorphine is a potent, long-acting narcotic agonist and antagonist and may be useful as a replacement for methadone treatment in addiction
  - Buprenorphine + Naloxone = Suboxone
  - Partial mu agonist
  - Slow onset, weak agonist.
  - Buccal film, transdermal patch, tablet
  - Maintenance treatment of moderate to severe opioid use disorder
  - Less euphoria, physical dependence, ceiling effect, milk withdrawal
  - Higher affinity for receptor than other opiates
  - RID= 0.09 – 2.52%

Hydrocodone

- Hydrocodone
  - Potency (1.5-2 X morphine)
  - 30 fold less active than its active metabolite Hydromorphone.
  - Subject to rapid metabolism, but still good choice.
  - The total dosage to infants was estimated at 0.7% of their neonatal therapeutic dose, suggesting that standard maternal doses are clinically irrelevant to the infant.

  - Hydrocodone is still generally recommended that for treatment of postpartum pain, and doses should be limited to no more than 30 mg/day. If higher doses are required, then the infant should be closely monitored for possible untoward complications such as sedation and apnea. Doses more than 40 mg/day should be avoided.[8]

  - **RID= 2.21% - 3.7%**

1. Sauberan JB, Anderson PO, Lane JR, et al. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. *Obstet Gynecol*. 2011 Mar;117(3):611-617.

Fentanyl

- 50-100 times more potent than morphine
- In a group of 10 women receiving a total dose of 50 to 400 µg fentanyl IV during labor, the concentration of fentanyl in milk was generally below the level of detection. In a few samples, the levels were between 0.05 and 0.15 ng/mL. Using this data, an infant would ingest less than 3% of the weight-adjusted maternal dose per day.
- In another study of 13 women who received 2 µg/kg IV after delivery and cord clamping, fentanyl concentration in colostrum was extremely low.[3] Peak colostrum concentrations occurred at 45 minutes following intravenous administration and averaged 0.4 µg/L.
- In a study of 5 women undergoing surgery with midazolam premedication and induction with propofol and fentanyl, milk samples were obtained at 5, 7, 9, 11, and 24 hours post fentanyl administration. The median amount of fentanyl recovered in milk within 24 hours post-dose was 0.024 µg or 0.024% of the maternal dose (100 µg). The weight-normalized infant dose was 0.005 µg/kg. None of the infants were given their mothers' milk during this study.
- RID =2.9% - 5%
- OK in healthcare setting. DANGEROUS in other settings.

Other Opiates Used and Abused

- Oxycodone
  - Potency (1.5-2 X morphine)
  - Significant euphoria
  - Highly addictive
  - 5-10 mg every 6 hours as needed.
  - RID= 1-4.56%
- Fentanyl
  - Potency = 80-100 X morphine
  - Rapid onset, short half-life
  - 25-35 µg IV every 30-60 min as needed.
  - RID= 2.9-5%
- Hydromorphone (Dilaudid)
  - Not metabolized to more potent metabolite
  - Potency (7-10 X morphine)
  - Caution in breastfeeding mothers
  - RID = 0.67%
  - Following dose of 4 mg q 4 h, respiratory depression in 6 day old breastfed infant.
  - Naloxone provided recovery.

Analgesics Overview

- Hydrocodone, morphine are generally safe in breastfeeding mothers.
- Codeine use still controversial, but probably safe in most moms
- Avoid High doses of Oxycodone (apnea).Highly addictive.
- Fentanyl levels in milk are low. Urine levels in infants are measureable, but may not be relevant.
- Buprenorphine is a potent, long-acting narcotic agonist and antagonist, but probably quite safe. RID = 0.09 – 2.52%
- Tramadol: Probably safe. Levels minimal, RID =2.86%
- Ibuprofen, Ketorolac, and acetaminophen are Ok
- Meperidine is poor choice due to neonatal sedation, neurobehavioral delay. But when used minimally, OK.

Gabapentin (Neurontin)

- Gabapentin is an older anticonvulsant formerly used for partial (focal) seizures with or without secondary generalization. It is also NOW primarily used for postherpetic neuralgia or neuropathic pain.
- Significant Withdrawal. Requires prolonged weaning.
- Doses range 600 – 3200 mg/day
- RID = 2.3%-6.5%
- Thus far, no untoward effects noted, and infant plasma levels seem very low to undetectable.
- In five mother/infant pairs(dose 900-3200 mg/day) RID = 1.3-3.8%
- Gabapentin advantage is it has a relatively wide therapeutic index.
- Symptoms of overdose: CNS depression (e.g. dizziness, drowsiness, slurred speech, lethargy, loss of consciousness) and gastrointestinal symptoms such as diarrhea.

Pregabalin (Lyrica)

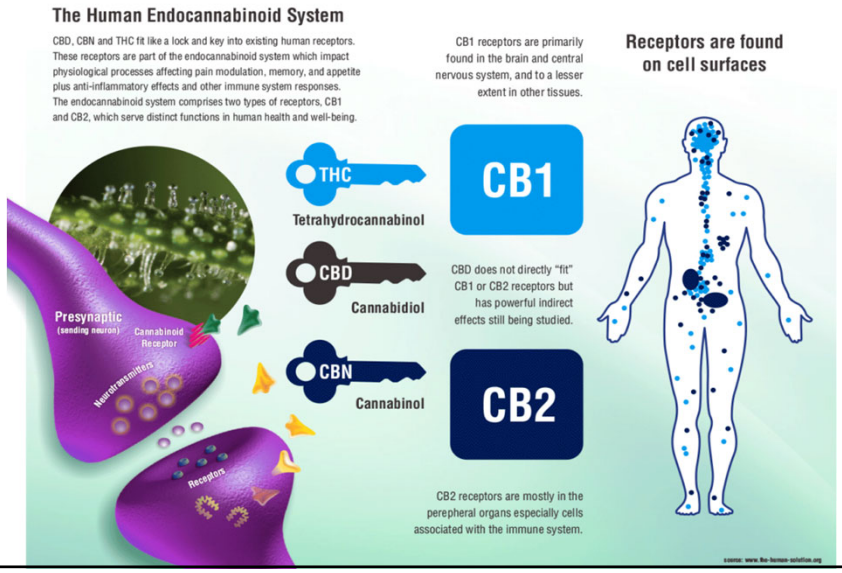
- Pregabalin is an anticonvulsant with multiple clinical indications, including partial seizures, fibromyalgia and neuropathic pain.
- As opposed to Gabapentin, pregabalin is well absorbed.
- No protein binding.
- Side effects: vertigo, dizziness, balance disorder, incoordination, ataxia, blurred vision, diplopia, amblyopia, somnolence, confusional state, tremor, disturbance in attention, abnormal thinking, asthenia, fatigue, euphoria, edema, peripheral edema, dry mouth, and constipation
- In a study of 10 healthy women (median 35 weeks postpartum) given pregabalin 150 mg twice daily for four doses, milk levels peaked at 4.63 hours.[1]
- Milk/plasma ratio was 0.53. T1/2=6.3
- Significant Withdrawal noted in adults.

- **RID =7.18%**

Other Analgesics

- Ketamine (Intranasal 28 mg)
  - Pain Surgical Pain Control
    - Rapid Acting Analgesic. Few hemodynamic problems.
    - Excellent analgeis with minimal respiratory problems.
    - No data are available on the transfer of ketamine into human milk.
    - Rapid redistribution out of plasma in 10-15 minutes.
    - Short half-life of 2.5 hours. It is poorly oral bioavailable.
  - GREAT for treatment-resistant depression
  - Esketamine Nasal spray. Just FDA approved
    - Side Effects: Sedation, dissociation, hypertension
    - **Levels in milk are likely LOW**. (Need samples)
- Dexmedetomidine
  - Dexmedetomidine is a selective alpha-2 adrenergic agonist used for sedation of initially intubated and mechanically ventilated patients in the intensive care unit and sedation of non-intubated patients prior to and/or during procedures.
  - Infusion in one breastfeeding mom(Mayo Clinic), levels in milk ranged from 15 – 89 picograms/mL.
  - Dose 45 µg stat, followed by 0.7 µg/kg/hour
  - Doses in milk are exceedingly low.

The Endocannabinoid Nervous System

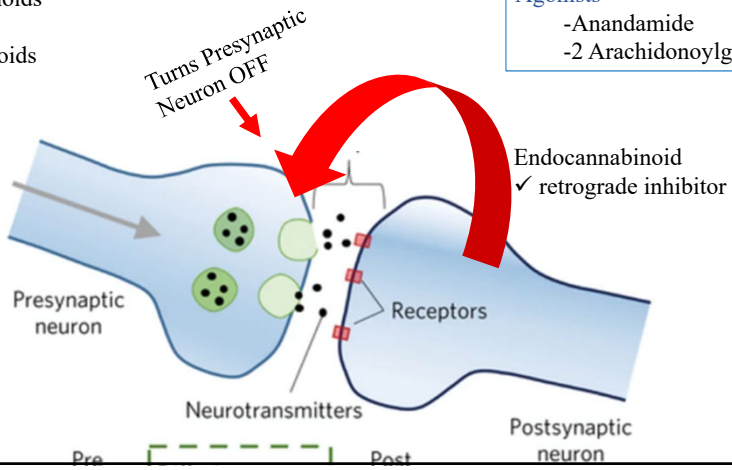


Phytocannabinoids and Endocannabinoids

Phytocannabinoids
(Marijuana)
Endocannabinoids

In Humans

ENDOCANNABIINOIDS
Agonists
-Anandamide
-2 Arachidonoylglycerol



Role of the endocannabinoid system

The role of the endocannabinoid system (ECS) in the human brain is to influence synaptic communication between neurons and also to control other processes such as eating, anxiety, pain control, learning and memory, reproduction, metabolism, growth, and development.

The ECS also has a role in weight gain, by inducing lipogenesis and increasing insulin resistance. One of the other roles of the ECS is to reduce both neuropathic and inflammatory pain.

Diseases Presently being treated with Cannabis

- Anorexia
- Nausea/vomiting
- Neuropathic pain
- Inflammation
- Multiple sclerosis
- Neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease)
- Epilepsy
- Glaucoma
- Osteoporosis
- Schizophrenia
- Cardiovascular disorders
- Symptoms of Cancer
- Metabolic syndrome-related disorders

Health Risks associated with Cannabis use.

- Respiratory Disease
  Chronic Cough, phlegm production, and chronic bronchitis. COPD
- Motor Vehicle Collisions
  Available data suggest that driving under the influence of cannabis indicated by self-report or the presence of THC in bodily fluid is associated with significantly higher odds of an MVC.
  Cannabidiol is not known to have psychoactive activity and is likely not associated with increased risk for MVCs.
- Lower Birth Weight Offspring
  Endocannabinoids are involved with critical steps in neurodevelopment. Cannabis use during pregnancy is linked to lower birth weight infants. Earlier in utero exposures to cannabis may affect organogenesis, and later in utero exposures may affect fetal growth.
  Data conflicted with co-use of cigarettes and alcohol.
- Psychosis
  Reported but at HIGH DOSES.

Older Breastmilk Studies

- Mother who smoked Cannabis **once daily** for 7 months, up to 105 µg/L of THC was quantified in her milk.[1]
  - Her infant had negative urine samples and was reported to have normal development by the pediatrician.

- Another Mother who used Cannabis **7 times per day** for 8 months was found to have 340 µg/L of THC.
  - In her second milk sample she had 60.3 µg/L of THC. **M/P ratio = 8**.
    - Her infant had negative urine samples but positive fecal samples for 347 ng of THC. This infant was also reported to have normal development by the pediatrician.
- Another mother using unknown amount had 86 µg/Liter milk.[2]

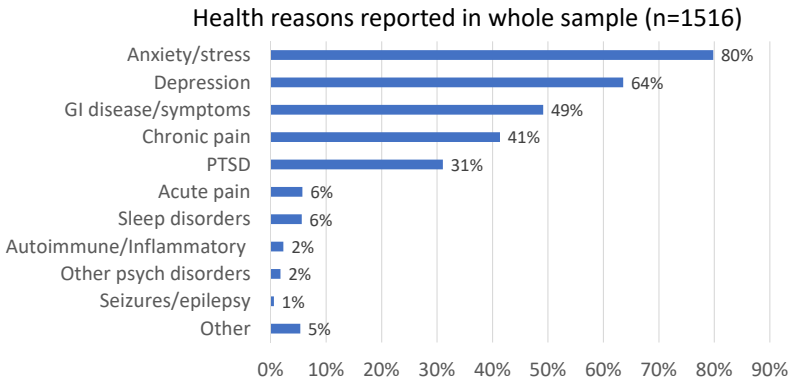
1. Perez-Reyes M, Wall ME. N Engl J Med 1982;307(13):819-820.
2. Marchei E, Escuder D, Pallas CR et al. J Pharm Biomed Anal. 2011.

Cannabis Use During the Perinatal Period in a State With Legalized Recreational and Medical Marijuana: The Association Between Maternal Characteristics, Breastfeeding Patterns, and Neonatal Outcomes.

- 3,207 respondents from the 2014-2015 Colorado Pregnancy Risk Assessment Monitoring System with state-developed questions on cannabis
- Pregnancy: Self reported prevalence: 5.7%
- Postpartum prevalence: 5%
- Prenatal cannabis use was associated with a 50% increased likelihood of low birth weight, independent of maternal age, race/ethnicity, level of education, and tobacco use during pregnancy.
- Small for gestational age, preterm birth, and neonatal intensive care unit admission were not associated with prenatal cannabis use, independent of prenatal tobacco use.

Crume TL, Juhl AL, Brooks-Russell A, Hall KE, Wymore E, Borgelt LM. *J Pediatr*. 2018;197:90-96.

Health reasons reported for cannabis use among breastfeeding mothers



Evidence that Cannabis Works ?

- **Good or Substantial Evidence**
  - **Treatment of chronic pain in adults (cannabis)**
  - **Anti-emetic for chemotherapy-induced nausea & vomiting (oral cannabinoids), FDA-approved**
  - **Improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)**
- **Moderate evidence**
  - **Improving short-term sleep outcomes in obstructive sleep apnea syndrome, fibromyalgia, chronic**
  - Some evidence with Lennox-Gastaut syndrome and Dravet syndrome

Hyperemesis Syndrome

- History of regular cannabis use for over a year (74.8%)
- HIGH Doses
- At least weekly cannabis use (97.4%)
- Severe nausea and vomiting (100%)
- Abdominal pain (85.1%)
- Vomiting that recurs in a cyclic pattern over months (100%)
- Resolution of symptoms after stopping cannabis (96.8%)
- Compulsive hot baths/showers with symptom relief (92.3%)
- Male predominance (72.9%)
- CHS is primarily associated with inhalation of cannabis
- Episodes generally last 24–48 hours, but may last up to 7–10 days.

Active Forms of Cannabis

- **Delta-9-THC**
- **Psychoactive component of Cannabis.**
- **Activates CB1 and CB2 receptors**

- **11-Hydroxy THC**
  - **Psychoactive component of Cannabis.**
  - **Slowly produced by liver**
  - **Activate CB1 and CB2 receptors**

- **Cannabidiol (CBD)**
  - **Non-psychoactive**
  - **Actually counteracts psychoactive impairment from THC.**
  - **Does not act at CB1 or CB2**
  - **Acts at GPR55 (cannabinoid receptor) and 5-HT1a receptors instead**

Cannabidiol (CBD)

- Non-psychoactive constituent of Cannabis Sativa Plant
- Suggestions that it moderates side effects of THC
- Does produce:
  - Neuroprotective ???
  - Anticonvulsant: treatment-resistant epilepsy (Dravet syn, Lennox-Gastaut syndrome.
  - Analgesia (in chronic pain syndromes)
  - Sedation
  - Anti-emetic
  - Anti-spasmodic
  - Anti-inflammatory effects
  - Anti-anxiety

Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers. 2007 Aug;4(8):1770-804. Review. PubMed PMID: 17712819

Cannabidiol (CBD)

- Oral absorption (< 1-5%) High First Pass effect in Liver
- Aerosolized CBD yields rapid peak plasma concentrations in 5–10 minutes and ~31% bioavailability.
- Huge Volume of Distribution. 32 L/Kg
- Plasma levels (@10mg/kg) = 5.9-11 ng/mL
- T1/2 = 18-32 hours
- Numerous Drug-Drug Interactions (inhibits CYP3A4, etc.)
- Does NOT activate CB1 and CB2 receptors
- CBD Exhibits
  - Neuroprotective (Reduces THC psychosis)
  - Antiepileptic anxiolytic
  - Antipsychotic
  - Anti-inflammatory properties
- NO Data on Breastmilk levels

Has the Strength of THC increased DOSE consumed ?????

600 mg Cannabis = 4-5%
= 24-30 mg THC

0.1 gm Cannabis = 23 mg THC)

0.1 gm (23%) = 23 mg

Intense heat volatilizes THC more rapidly in pipes (also wastes more)

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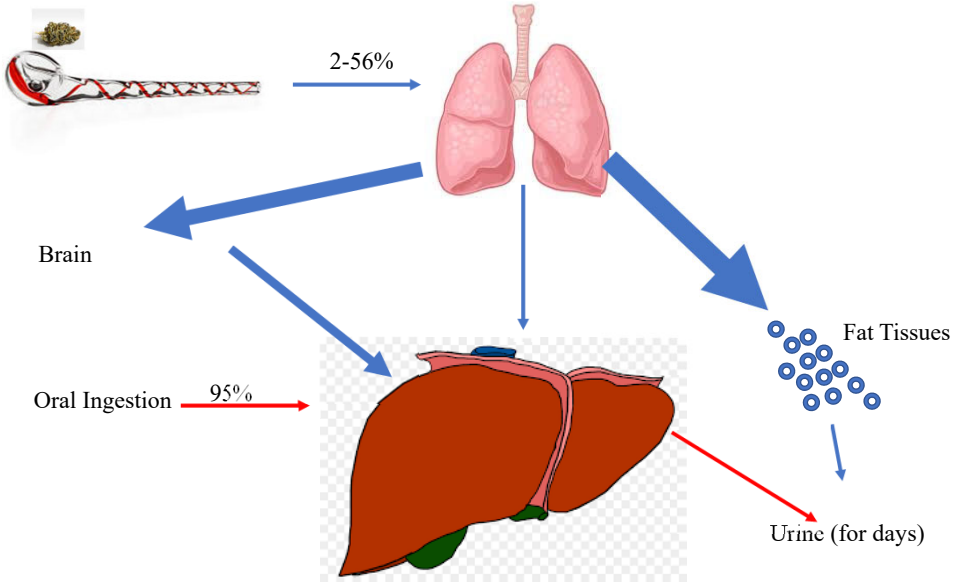
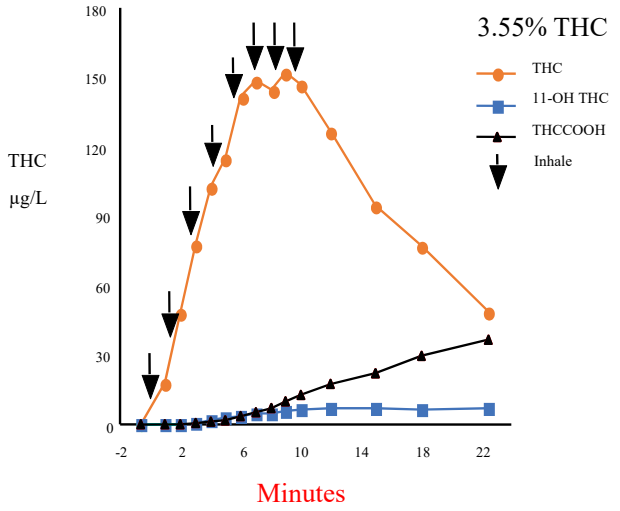
Compartmentalization of Cannabis



THC, 11-OH-THC & THCCOOH Plasma Concentrations After Smoking Cannabis



THC detected 3 - 27 h

THCCOOH 2 – 7 days

Huestis et al

J Anal Toxicol 1992

ORAL Absorption

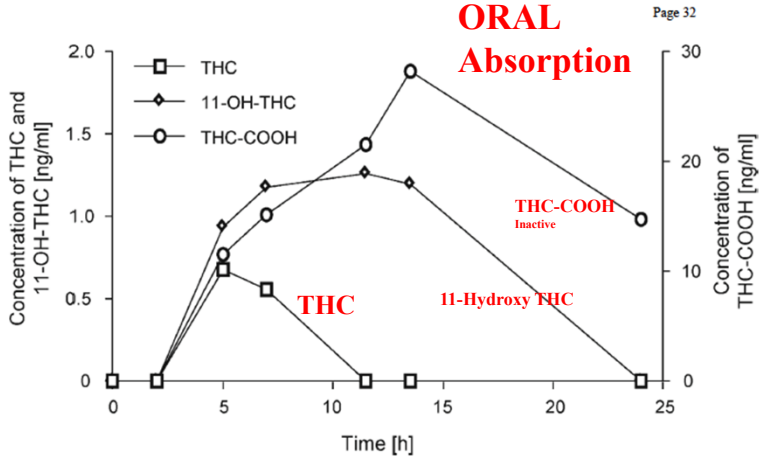


Fig. 3.
Plasma concentrations (N=1) over 24 h for THC, 11-OH-THC, and THC-COOH following administration of two doses (2.5 mg each) of synthetic THC (dronabinol) at 4.5 and 10.5 h.
Reprinted and adapted with permission by Elsevier, p. 152 in [32], Fig. 2.

Marijuana Kinetics

- **Slow release from Adipose and Liver and Enterohepatic recirculation (10-15%) contributes to long estimates**
  - **Rapidly redistributes to Adipose**
  - **T1/2 = 4.1 days in chronic users, maybe longer.**
  - **Terminal URINARY excretion of THC-COOH = 6.2 days**
- **Absorption:**
  - **Inhaled is highly variable (2-56%) due to variability in smoking dynamics**
    - **Mean Peak average 162.2 ng/ml (range 76– 267) with 3.55% cigarette.**
    - **Peaks in 10-20 minutes depending on how smoked**
  - **Oral absorption complete = 90-95%**
    - **BUT: 95% sequestered in liver and metabolized. Never reaches plasma**
    - **Peak = very slow (1-2 hours)**
      - **Huge Volume of Distribution (adipose tissue, liver, etc)**
- **Plasma levels drop rapidly to 10% of peak in 3-4 hours and are generally < 1 ng/mL**

What does Drug Screening tell you ?

It tells you you've been exposed to MJ sometime in the last 2-4 weeks.

Phase 1

- Subject smokes, orally ingests, or uses topically Cannabis Product
- Plasma levels are moderate

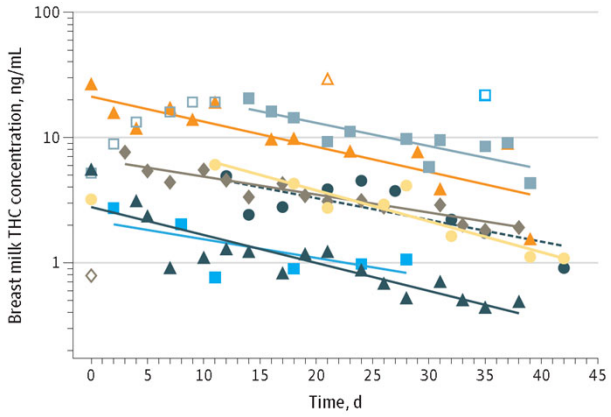
Phase II

- THC and metabolites transfer to plasma, then CNS, then liver and adipose
- Most THC is metabolized
- Most THC transfers to adipose tissue and is stored
- **After 30 minutes plasma levels < 1 ng/mL**

Phase III

- THC leaks out of adipose and other compartment in miniscule amounts
- Plasma levels are all but undetectable.
- Picked up by kidney
- Concentrated in Urine

Daily infant dosage, median (interquartile range), µg per day	2	6.7	0.7	2.4	0.6	2	6.8



µg = one millionth of a gram. Average dose in milk = 3 µg/ day.

If Mom smoked once daily (≅ 20,000 micrograms of THC:

Baby ingests 3 µg/day

Infant received ≅ 3 µg or 0.015 percent of dose. *Further, infant oral absorption is ≅ 1-5% of dose.

The milk:plasma partition coefficient for THC was approximately 6:1

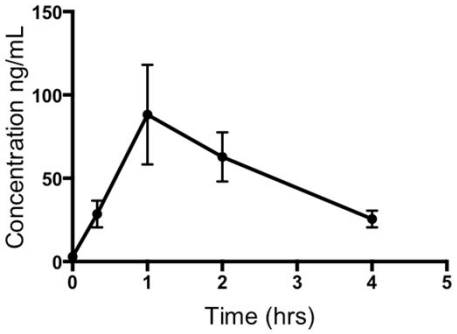
Wymore EM, Palmer C, Wang GS, Metz TD, Bourne DWA, Sempio C, Bunik M. Persistence of Δ-9-Tetrahydrocannabinol in Human Breast Milk. JAMA Pediatr. 2021 Jun 1;175(6):632-634. doi: 10.1001/jamapediatrics.2020.6098. PMID: 33683306; PMCID: PMC7941249.

Transfer of Inhaled Cannabis Into Human Breast Milk

To evaluate the transfer of Δ^9-THC and its metabolites into human milk at 20 min, 1, 2 and 4 hours after maternal inhalation of 0.1 g cannabis containing 23.18% of Δ^9-THC.

Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem RR, Hale TW. Transfer of Inhaled Cannabis Into Human Breast Milk. Obstet Gynecol. 2018 May;131(5):783-788. PMID: 29630019.

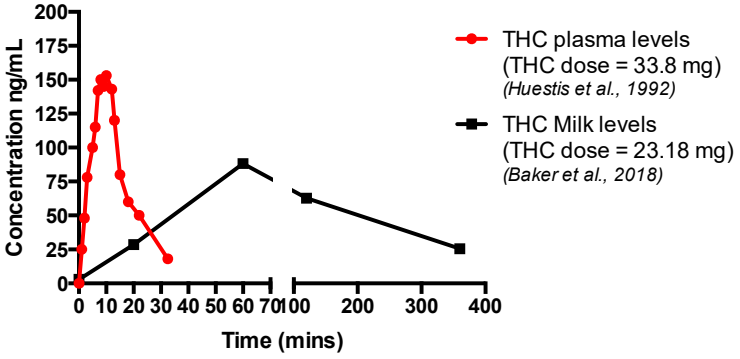
Results:

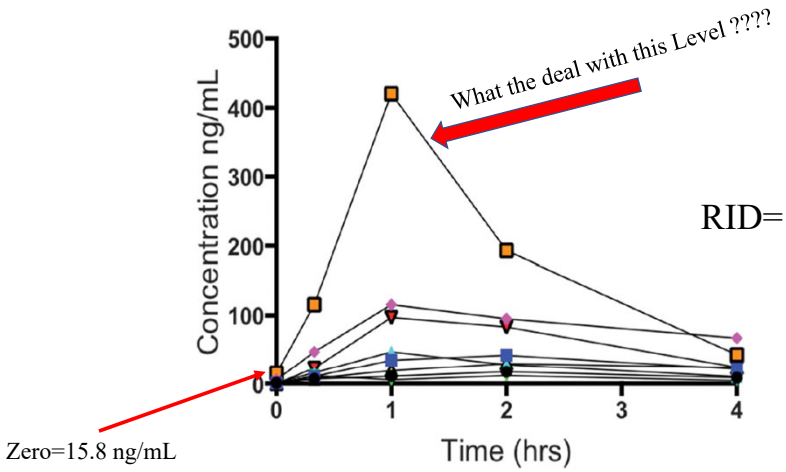


Mean concentration-time profile of delta-9-THC in human milk (Mean ± SEM, n=9)

Parameter (units)	**Value**
AUC (ng.h/mL)	208.2
C_{avg} (ng/mL)	52.05
C_{max} (ng/mL)	88.21
T_{max} (h)	1
Infant dose (µg/kg/day)	7.8
RID (%)	2.4

Comparison of PLASMA and MILK Curves





RID= 0.3 to 8.7%

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

Baker. Inhaled Cannabis in Human Breast Milk. Obstet Gynecol 2018.

Questions that still need answering:

1. What are the kinetics of oral absorption of Δ^9-THC in the infant ?
2. What effect would repeated and continuous doses have on milk levels?
3. How much Δ^9-THC would transfer into mother's milk following the use of ORAL cannabis products?
4. Do exogenous cannabis products affect the Endocannabinoid signaling system ?
5. What is the lasting impact of exposing developing infants to cannabis?

Final Thoughts

- With Opioids and Cannabis it's a wrestling match between the BENEFIT of human milk against the DETRIMENT of opioids and cannabis.
- The Reality is that with HIGH DOSES of Opioids you must be careful
- In Chronic/Dependent Moms, the infant is Less Sensitive to opioids and continued breastfeeding may actually reduce withdrawal in the infant without risk of apnea.
- In NON-Dependent Moms, infant is at higher risk of apnea depending on dose.
  - Introduce lower doses of milk (half and half Donor milk) for week or so to allow baby to clear plasma levels of Opioid.

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