Pharmacokinetics of Cannabidiol (CBD)

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Conflict of Interest Statement

- Past year paid consultant or advisory board member: Mira1a Therapeutics, Jazz Pharmaceuticals, Syqe Medical Ltd., WebMD, Charlotte’s Web
Overview of Talk

- Metabolic pathway
- Impact of route of administration
- Impact of product formulation
- Gastric contents
- Drug interactions
- Liver function/toxicity

Cannabidiol (CBD)
Cannabidiol (CBD) Metabolism

- CBD is metabolized by the liver via CYP450 oxidases, glucuronyl transferases and sulfotransferases (1).
- The CYP450 enzymes involved include CYP1A1, CYP1A2, CYP2C19, CYP2D6, CYP3A4, CYP3A5, AND CYP2A9.
- Glucuronidation of CBD at the phenolic oxygen is the primary Phase II biotransformation mechanism, but hydroxylation and sulfation can also occur (1).
- ~40 metabolites have been identified; 7-COOH-CBD is primary metabolite in human blood; 7-OH-CBD is primary in human urine (1).
Cannabidiol (CBD) Metabolism

• Differences in metabolism have been noted in pre-clinical models.
• In human *in vivo* studies, 7-COOH-CBD concentrations in plasma far exceed that of the parent CBD.
• In rodents, 7-COOH-CBD concentrations are comparable to parent CBD and 6-COOH-CBD is more abundant.
• Rabbits best approximate human 7-COOH-CBD:CBD ratio.
• Dogs—less 7-COOH-CBD than parent CBD; 6-OH-CBD primary (2).
• Thus, pre-clinical models are limited with respect to CBD metabolism and may have altered outcomes related to toxicity.
Variation by Route of Administration

- Retail CBD products vary and are intended to be smoked, vaporized, orally ingested, topically applied, or inserted
- Route significantly impacts bioavailability and time course
- Controlled laboratory studies conducted at the Johns Hopkins Cannabis Science Laboratory (3-8)
  - Healthy adult volunteers
  - No past month exposure to cannabis or CBD
  - Acute dosing
  - Assessments pre- and post-dosing
Variation by Route of Administration—Acute Dose

- Blood CBD time course
- Blood 7-COOH-CBD time course
Variation by Route of Administration—Acute x Sex

Female

- Oral CBD
- Vaped CBD
- Topical CBD

Male

- Oral CBD
- Vaped CBD
- Topical CBD

Blood CBD (ng/mL) vs Time (hours) for both female and male groups.
Variation by Route of Administration—Acute AUC

![Graph showing variation in AUC by route of administration with bars for Oral CBD, Vaped CBD, and Topical CBD.]
Relating PK to PD with Cannabinoids

Blood Delta-9-THC levels vs subjective drug effects at 25mg
Variation by Route of Administration—14-day BID
Variation by Route of Administration—14-day BID

- Urine CBD (ng/mL)
- Urine 7-OH-CBD (ng/mL)
- Urine 7-COOH-CBD (ng/mL)

Time (hours): BL 0.5 1 1.5 2 3 4 5 6 24 48 168 240 336 408 504

- Oral CBD represented by circles
- Topical CBD represented by triangles
Variation by Formulation

• Oral and topical CBD products vary considerably by the matrix in which the drug is contained
• Oral products: gummies, oils, beverages, capsules, hard candies, every kind of food product; some instruct for buccal absorption
• Topical products: creams, lotions, patches, salves, gels, balms, shampoo, cosmetics, etc.; may contain permeation enhancers
Variation by Formulation—Oral Matrix
Variation by Formulation—Effect of Food

- Gastric contents shown repeatedly to impact CBD absorption above and beyond matrix.
- High fat foods facilitate CBD absorption (9).
- Consumption on empty stomach results in very low absorption (5, 10).
- Little evidence that stomach pH or acidic food results in meaningful conversion of CBD to THC (4, 11).
Variation by Formulation—Sesame Oil vs. MCT Oil

![Graph showing blood CBD levels over time for Epidiolex and CBD Alone formulations.](image-url)
Variation by Formulation—Topicals

- Controlled study of 5 different topical CBD products (8); lotion, balm, patch, gel, cream
- Low levels of CBD absorption (CBD detected after acute lotion only)
- Absorption was impacted by permeation enhancers (e.g., DMSO, EtOH)
- Patch and balm showed no blood cannabinoids after 10 days of use
- Accumulation with repeated use in lotion, cream and gel
Variation by Formulation—Vaped CBD vs. CBD+THC
Variation by Formulation—Vaped CBD vs. CBD+THC

- With vs without THC – 2012 oral and 1805 vaped
Variation by Formulation—Oral CBD vs. CBD+THC
Variation by Formulation—Oral CBD vs. CBD+THC

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
Drug-Drug Interactions (7)

- N = 20
Drug-Drug Interactions

- Package insert for Epidiolex recommends:
- Dose reduction with concomitant use of moderate or strong inhibitors of CYP3A4 or CYP2C19
- Dose increase with concomitant use of moderate or strong inducers of CYP3A4 or CYP2C19
- Dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19; possible dose adjustment for substrates of CYP1A2 and CYP2B6
Liver Function

- Dose reduction required for moderate-severe hepatic impairment
- Elevated liver enzyme levels observed in some clinical trials; most were associated with concomitant use of clobazam or valproate
- Meta-analysis of 28 clinical trials (12) showed adverse liver enzyme effects were associated with:
  - CBD exposure ≥1,000 mg/day or ≥20 mg/kg bw/day
  - Concomitant use of Valproate
- No cases of severe drug-induced liver injury were identified in any of the 28 studies.
Conclusions

• CBD metabolism/excretion achieved through a variety of mechanisms and varies by species
• Pharmacokinetics significantly impacted by route of administration and formulation
• Oral dose impacted significantly by gastric contents
• CBD inhibits several CYP450 pathways resulting in clinically significant drug interactions – may require dose adjustments
References


References


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