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Cannabis Pharmacokinetics: Considerations for Dose, Absorptions, Bioavailability



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Cannabis Is a Holistic Plant

- Pharmacokinetics typically concerns pharmaceuticals
- Dynamic, holistic plant
- THC = plant-derived potent drug
- Dynamic tension between botanical + pharmaceutical sides of plant





Recommendations Dependent on Variables

- Use an herb or plant in its most traditional whole plant form – more synergistic effects, more diffuse benefits, improved safety profile
- Extracted drug preparation → extracted + concentrated active principles
 - More targeted, better able to measure dose + effects
 - Greater risks for side effects + possibly overdose
 - Some patients require high doses of active plant constituents





Science of Pharmacokinetics

- Useful to practitioners + patients
 - What cannabis preparation to use
 - What route of ingestion
 - Provides tools for predicting the effects of preparations
 - Helps reduce unwanted effects





What Is Pharmacokinetics?

- Science of what the body does to a drug
- Specifically addresses the dynamics of a drug's (ADME)
 - **A**bsorption
 - **D**istribution in the body once absorbed
 - **M**etabolism by the body (how the body converts + processes a drug)
 - **E**limination, or excretion, of a drug (respiratory, fecal excretion, urine excretion)





What Affects Pharmacokinetics?

- Physiochemical property of the molecule
 - Large or small
 - Ionized or non-ionized
 - Acidic or basic
 - Lipo-soluble or water-soluble
- Properties of human membranes
 - Passive transport
 - Receptive, or active-mediated, transport





What Affects Pharmacokinetics?

- Chemistry of the body
- Stomach acidity
- Metabolism, such as liver enzymes
- Body chemistry
- Genetic polymorphisms
- Environmental factors, such as stress
- Age + gender, pregnancy status





What Is Half-Life ($t_{1/2}$)?

- Time it takes for the plasma concentration of a drug to be reduced by half
- A compound with a long half-life can take hours or even days to be reduced by half
- Short half-life can be minutes, sometimes even seconds
- Reveals a bit about the character of the drug
- A drug with a longer half-life does not necessarily equal longer effects.





Volume of Distribution (Vd)

- Extent to which a drug travels to tissues outside the bloodstream
- Vascular compartment (blood vessels) = average blood volume of 5.5 liters
- Small volume of distribution of a drug → remains at about 5 liters in the bloodstream with no to little affinity for the tissues
- Large volume of distribution





Other Pharmacokinetic Terms

- C-Max (C_{max}) = maximum concentration of drug in the bloodstream (bioavailability)
- C-Max steady state (C_{maxSS})
 - Maximum concentration of the drug in the bloodstream that is achieved after consecutive dosing at a constant rate.
- T-Max and T-Max steady state (T_{max}, T_{maxSS})
 - The amount of time after initial dose or consecutive doses of C_{Max} + C_{Max} steady state, respectively





Pharmacodynamics Quick Explanation

- What the drug does to the body
- Cannot always be measured directly, such as measuring reduction in pain or depression
- Primary focus typically on effects of drugs rather than the dosing
- Understanding of pharmacokinetic principles offers best practice guidelines
- Accurate dosing is not always essential to achieve a desired + predictable outcome
- With THC specifically, research shows a lot of variability in dose and effect among individuals





Inter-Individual Variation for THC

- Use general guidelines of pharmacokinetics for choosing a dose, dose form + administration route for most predictable + desirable effects
- Unique molecule, yet we do not know why!
- Clinical trials of synthetic (but bio-identical) THC, dronabinol, revealed that 5 mg given to two patients with same gender, genetics, weight, etc will not necessarily have the same effects
- THC + cannabis used as medicine require customization, personalized medicine





Linear Pharmacokinetics

- Administer a THC dose + measure in the blood
- Increase the dose + measure a requisite increase of the THC in the blood
- As the dose increases, the amount of THC in the blood increases
- THC dosing shows some predictability: higher doses result in higher amounts in the bloodstream → greater delivery to the tissues → greater effect both subjectively (pain relief, intoxication) + objectively (measurements of heart rate, blood pressure)





THC Absorption

- Rate at which a drug exits it's site of administration
 - Inhaled dried flower → measure the rate at which THC enters the bloodstream after smoke enters the lungs
 - Ingested form of cannabis (edibles + tinctures) → measure the rate at which THC enter the bloodstream after it enters the stomach + liver





THC Bioavailability

- Extent to which an administered dose reaches an area or site of action
- Generally, the first stop is the bloodstream
- Any drug administered intravenously automatically has a bioavailability of 100%
- 100% of bioavailability is impossible with oral administration





First Pass Effect

- Anything that goes through the stomach automatically goes through the liver
- What happens to the drug after it goes to the liver
- Large first pass effect the liver = inactivates most → less active drug in the bloodstream
- Small first pass effect = more drug available in the bloodstream to potentially access the sites of therapy





THC Absorption via Inhalation

- Detected in plasma virtually immediately
- Bioavailability: 2% to 56%
- Variables that impact bioavailability
 - Inter-individuality in inhalation
 - Medicine lost to the air in side-stream smoke that's not inhaled





Cannabis Inhalation

- C-Max achieved (maximum THC concentration in bloodstream) in about 10 minutes
 - Inhalation delivers the drug rapidly to the bloodstream
- Blood transfers THC rapidly to the tissues including the brain
- Efficient way to introduce cannabis to the bloodstream + quickly gauge its effects
- Compares very well to intravenous administration





Sublingual THC Administration

- Advantageous because of blood vessels in the mouth
- Some of the drug is absorbed directly into the bloodstream
- Bypasses the liver, just like inhalation
- Drug enters the bloodstream much more quickly than oral dosing
- Sativex® – pharmaceutical spray of equal parts CBD and THC
- Under-used route of administration





Rectal THC Administration

- Special preparation of THC required in a more dissolvable salt form for bioavailability (13%)
- Pure THC is not bioavailable by this route
- Small study in humans compared oral + rectal routes
 - Rectal format twice as available
 - Resulted in lower blood levels
 - Lower C-Max
- Potentially under-used route worthy of further study





Topical CBD Products

- Scant published data
- Patient testimonials reported effects
- Molecular weight of THC = 314
- < 400 molecular weight is permeable in human skin
- For any THC topical, some of it will make it across the skin into the bloodstream
- For bioavailability, dosing + effects → only anecdotal data so far
- Route worthy of more investigation





Oral Administration

- THC preparations ingested through the stomach
- Data from the clinical trials from synthetic THC – dronabinol or Marinol®
- Data from standardized natural THC extract Namisol® (in the Netherlands)
- Data from THC whole plant extracts in food
- Most erratic kinetic levels in the bloodstream





Oral Administration

- Low bioavailability: about 6%
- Clinical trials on dronabinol: 10 to 20% bioavailability
- Significantly lower than inhalation
- C-Max: 2-6 hours
- Effect on the brains is delayed





Factors that Impact Cannabis Oral Absorption

- THC degradation in the stomach
- Stomach acidity degrades a portion of ingested THC
- A highly acidic stomach will degrade more THC
- A less acidic stomach will degrade less THC
- Stomach acidity decreases with age
- Frequently prescribed oral pharmaceutical antacids – H1 blockers: cimetidine, or Tagamet®; proton pump inhibitors: omeprazole, or Prilosec®; + OTC antacids (Tums)





Kinetics of Drug Distribution

- Movement of the drug from the bloodstream into the tissues (including outside or inside cells)
- Influenced by many factors – blood flow to the tissue, the tissue type + volume, the degree to which the drug binds to any tissue
- THC perfuses first into the lungs, then the kidneys, heart, liver adipose tissue, brain + muscle tissue





THC Is Highly Plasma Protein Bound

- Proteins in the bloodstream
- Some drugs have high affinity for these proteins + remain bound to them
- Bound drug is not active drug
- THC has a high affinity for tissues, especially fat plus most stays bound to plasma proteins
- High amount of THC remains in the bloodstream circulating + recirculating





Meds + Medical Conditions that Can Reduce Plasma Proteins

- Drugs (ie: aspirin, anti-seizure drugs)
- Kidney disease
- Hepatic disease
- Pregnancy
- Stress
- Trauma





THC Metabolism

- For oral dosing, metabolism means what happens in the liver
- First pass metabolism: metabolism of a drug by the liver prior to distribution
- Elimination metabolism: what happens to the drug after it goes through the liver once before distribution the tissues; how that drug eventually gets eliminated





Liver Metabolism

- Cytochrome P450 liver enzymes crucial for metabolizing most drugs
- Can have genetic variability: “poor metabolizers” versus “ultra-rapid metabolizers”
 - Poor metabolizer → higher drug impact
 - Ultra-rapid metabolizers → lower drug impact
- Lifestyle habits can induce or inhibit enzymes
 - Tobacco tends to induce liver enzymes
 - Alcohol requires more liver enzymes to metabolize





Inhalation (Vapor or Smoking) versus Oral Ingestion

- Liver converts THC into 11-hydroxy THC (11-OH-THC)
- After smoking or vaporizing, the liver is bypassed
- Small amount of liver metabolism from THC delivered the bloodstream
- From smoke or vapor: about 10% of a total THC dose converts to 11-hydroxy THC
- Orally ingested: the liver converts about 50% of a total THC dose to 11-hydroxy THC
- Equal blood levels of THC + 11-hydroxy THC prolong THC effects





11-Hydroxy THC

- Equally as potent as THC
- Crosses the blood-brain barrier more readily
- Not as protein bound
- More available to interact with tissues + interact with the brain





Effects of Smoke/Vapor Dosing

- Smoke or vapor results in instant titration + better ability to gauge effects
- Shorter duration if dose is too high
- Oral dosing more discreet, convenient
- Many patients cannot or should not inhale cannabis smoke or vapor
- Conservatism + caution warranted with respect to oral dosing with cannabis naïve, elderly + medically fragile patients





Effects of Oral Dosing

- Longer lasting + more extensive psychoactive effect from oral preparations
- More subject to interpersonal genetic + disease state variabilities
- Potential longer lasting positive effects (pain relief)
- Potential increased for accidental overdose and negative effects (paranoia, nausea)
- Crucial to evaluate a patient's age, gastrointestinal acidity, meds, plasma protein status, diseases, genetic metabolic issues





THC Excretion

- Most eliminated in the feces
- 20% in the urine
- In liver: 11-hydroxy THC → 11-nor-carboxy THC (inactive metabolite)





CBD Pharmacokinetics

- Attenuates some of the psychoactive effects of THC
- Mechanism as yet to be fully elucidated
- Does not antagonize THC
- Does not act readily at endocannabinoid receptors
- Similar absorption profile to THC
- More extensively metabolized in the liver
- Ties up CYP P450 enzymes more than THC
- May possibly interact with more prescription drugs, especially at high or chronic doses





Further Research Topics

- Dose response – cannabis naïve patients; CO2 + BHO concentrates
- Topical preparations/rectal preparations
 - Benefit to the tissues even if effects are not felt in the brain?
 - Delivery forms: (fat-soluble vehicle versus water-soluble one can affect how much of a dose is absorbed)
- Micro-dosing
- Carbocyclic acid forms of cannabinoids (THCA + CBDA)
- Form of cannabinoids found prior to heating the plant
- Primary cannabinoids in cannabis juice + other cold, fresh preparations of the plant

