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Cannabis: Pharmacology, Psychoactive Agents and Drug Interactions

Ureh Nena Lekwauwa, M.D., D.F.A.P.A.

Introduction

Cannabis or marijuana is the most commonly used illegal substance in the world and approximately four percent of the world's population has used cannabis at least once in the past year (Leggett). Herbal cannabis contains over 400 compounds including 60+ cannabinoids that are aryl-substituted meroterpenes from the plant genus *Cannabis* (Ashton). Cannabidiol (CBD) is one of the 60 active cannabinoids identified in cannabis (Borgelt). As a major component of the plant, CBD accounts for up to 40% of the plant's extract, as a non-psychotropic phytocannabinoid. Pharmacology for most of the cannabinoids is largely unknown but the potent psychoactive agent, tetrahydrocannabinol (THC) is the major psychoactive agent that has been isolated, synthesized, and studied. The effects of THC are dose-related and most research on cannabis was established in 1970's using smaller doses of 5-25 mg THC; therefore, the risks and consequences of today's marijuana use may be unknown because sophisticated cultivation in the past 30 years increased the potency of cannabis products. In 1960s and 1970's average "reefer" contained about 10 mg THC (Ashton). Now "joints" made of skunkweed, netherweed, and other potent subspecies of *Cannabis sativa* can contain up to 150 mg of THC (or 300 mg if laced with hashish oil). Today's cannabis smoker may be exposed to THC doses many times greater than in the past. For every cannabis user who develops a dependency, in DSM-5 terminology -a moderate to severe cannabis disorder, ten users do not (Bailey).

Cannabis Pharmacology

Pharmacokinetics

Fifty percent of THC in a smoked joint is inhaled and nearly all is absorbed through the lungs, rapidly entering the blood stream and reaching the brain in minutes. The effects are perceptible within seconds and fully within minutes. With oral ingestion, bioavailability is lessened and blood concentrations reach 25-39% of that obtained by smoking the same amount due to slow oral absorption and first metabolism in the liver. Once absorbed THC and other cannabinoids are rapidly distributed to all tissues at rates dependent on the blood flow.

Cannabinoids are extremely lipid soluble and accumulate in fatty tissues, reaching peak concentrations in four to five days and then are released slowly back into other body compartments including the brain. Because THC is sequestered in fat, THC tissue elimination half-life is about seven days and the complete elimination of a single dose may take up to 30 days. With repeated doses, high levels of cannabis accumulate in the body. In the brain, THC and other cannabinoids are differentially distributed – with high concentrations found in the neocortical, limbic, sensory, and motor areas (Ashton).

Cannabinoids are metabolized in the liver resulting in more than 20 metabolites - some are active and have long half-lives, the major one being 11-hydroxy-THC. Many metabolites are excreted in urine and some are excreted into the gut where they are reabsorbed and prolong cannabis actions. As a result of this delay and sequestering in fat, there is a poor relationship between plasma or urine concentrations and degree of cannabinoid-induced intoxication. The 11-hydroxy-THC is rapidly metabolized to the nonpsychoactive 11-nor-9-carboxy-THC (THC-COOH). A majority of THC is excreted via the feces (65%) with approximately 30% of the THC eliminated in the urine as conjugated glucuronic acids and free THC hydroxylated metabolites. At this point, THC becomes inactive or nonpsychoactive.

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Pharmacodynamics
The biological effects of cannabinoid compounds including marijuana are determined by their binding to and further activation of cannabinoid receptors (Manzanares). Cannabinoids exert their effects by interaction with specific endogenous cannabinoid receptors --CB1 and CB2. The distribution of CB1 follows the pattern of THC and includes cerebral cortex, limbic areas including hippocampus and amygdala, basal ganglia, cerebellum, thalamus and brainstem. THC increases the release of dopamine from the nucleus accumbens and prefrontal cortex. This effect, which is common to many drugs such as heroin, cocaine, amphetamine, and nicotine, may be the basis of its reinforcing properties and its recreational use. It is reversed by naloxone, suggesting an opioid link. THC binds to cannabinoid receptors and interferes with important endogenous cannabinoid neurotransmitter systems. Receptor distribution correlates with brain areas involved in physiological, psychomotor and cognitive effects. As a result, THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature.

THC is metabolized via cytochrome P450 2C9, 2C11, and 3A isoenzymes. Potential inhibitors of these isoenzymes could decrease the rate of THC elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Effects of Cannabinoids
The euphoria of inhaling cannabinoids comes within minutes of smoking and reaches a plateau lasting two hours or more, depending on dose. There can be dysphoric reactions such as severe anxiety and panic reactions. Paranoia and psychosis are also dose-related and more common in anxious subjects, “naïve” users, and psychologically vulnerable individuals.

Colors seem brighter, music more vivid, emotions more poignant and ‘meaningful’, and spatial perception is distorted. Time perception is impaired, and the ability to know the actual passage of time is flawed. Hallucinations may occur with high doses.

Cannabinoids also affect cognition and psychomotor activities. Effects are consistently dose-related even with long-term users. There is slowing of reaction time, motor incoordination, defects in short-term memory, and difficulty in concentration. There is also impairment in the ability to complete complex tasks that require divided attention. Driving and piloting skills are impaired. Furthermore, these effects are additive and compounded with other central nervous system depressants. Withdrawal symptoms include restlessness, insomnia, anxiety, increased aggression, anorexia, muscle tremor, and autonomic effects.

Physiologic effects impact cardiovascular conditions such as dose-related tachycardia of up to 160 beats/minutes or more. With chronic use although tolerance can develop, widespread vasodilation and reddening of conjunctiva and postural hypotension and fainting can still occur. These effects are risker for individuals with a predisposition to cardiac disease.

Respiratory issues include the herbal cannabis preparation that exposes individuals to more carbon monoxide, bronchial irritants, tumor initiators, tumor promoters and carcinogens than tobacco smoke - five times greater increase in carboxyhemoglobin, three times greater amount of tar inhaled and one-third more retention in the respiratory tract of tar than smoking a tobacco cigarette (Ashton). Chronic cannabis smoking is also associated with increased risks for chronic obstructive pulmonary disease.

Drug Interactions

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The issue of cannabis and drug interactions is extensive and two types of drug interactions are pharmacodynamic and pharmacokinetic.

Pharmacodynamic drug interactions occur when two drugs exhibit similar effects on the body. In this case, the central nervous system (CNS) sedation is the main action of cannabis and there are a multitude of drugs that can cause CNS sedation: benzodiazepine, antipsychotics, opiates, barbiturates, and others.

Pharmacokinetic drug interactions deal with how one drug can affect the absorption, distribution, metabolism and/or excretion of another drug. Each drug has a process of how the body "normally" handles the drug's absorption, metabolism, excretion, etc. A drug is absorbed at a specific rate and extent, distributed throughout the body at a certain volume, and metabolized and excreted at a certain rate. In the case of cannabis, it is an inhibitor of one of the main metabolic pathways (CYP3A4), as well as an inducer of another common metabolic pathway (CYP1A2).

If the metabolic pathway is inhibited, the other drugs that use the pathway will not get metabolized at a normal rate, and this can cause potential toxicity of that particular drug. As an example, a patient taking the anticoagulant warfarin (Coumadin®) and who decides to smoke marijuana, the warfarin metabolism may be inhibited, and the patient will accumulate a higher concentration of warfarin in the system and will be at risk for excessive bleeding.

If the metabolic pathway is induced, the other drugs that use the pathway will get metabolized at a faster rate that can cause therapeutic failure of the drug. For example, if a patient takes alprazolam (Xanax®), then starts to smoke cannabis, this will lead to a lower concentration of alprazolam which could to lead to withdrawal and possibly seizures.

Sometimes there could be two different mechanisms at work. In the case of the patient above for the first few days, the pharmacodynamic interaction of the additive sedation will predominate, and the patient will be over sedated but invariably the pharmacokinetic interaction will predominate resulting in lower serum concentration and less sedation.

Cannabis inhibits the CYP3A4 pathway, so all drugs that use CYP3A4 as a moderate to major pathway could be affected significantly. Furthermore, because a drug inhibits or induces the system does not mean it uses the system but substrates of CYP3A4 need to be considered. There are many "minor" substrates of this system, but these interactions are not clinically relevant. Also, the likelihood for drugs that are topicals or ophthalmics to interact is very low.

The cannabidiol-rich cannabis extract, CBD, has been shown to be widely effective for children with epilepsy. CBD and conventional anti-convulsant drugs have some similar action mechanisms. CBD has anti-seizure effects and better seizure control (Hill). It is suggested that CBD may block seizures by blocking the N-methyl-D-aspartate (NMDA) receptor, enhancing the gamma-aminobutyric acid (GABA) receptor, and stabilizing ion channels similar to mechanisms as Banzel, Lamictal, Dilantin, Keppra, and Trileptal (O' Shaughnessy). CBD also received orphan drug status in the US as an orally-administered liquid for the treatment of dravet syndrome (Wilner). Further research will help determine which types of epilepsy CBD is going to help, its side effects, and how it interacts with other anti-seizure drugs.

Summary

Chronic cannabis use results in tolerance, dependence, withdrawal, and long-term cognitive impairments. Long-term use carries respiratory, cardiovascular, and other health risks. Cannabis use is

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associated with adverse psychosocial problems and affects multiple organ systems. Many physicians, medical organizations, health care providers, government/elected officials, and individuals take differing views of the benefits and risks of medical cannabis but almost everyone agrees further research is needed.

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