ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

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Overview of Cannabinoid Derivatives

Background

Cannabinoid derivatives are naturally occurring or synthetic compounds that interact with the endocannabinoid system, producing a range of effects similar to delta-9-tetrahydrocannabinol (Δ^9-THC, or delta-9), the primary psychoactive component of cannabis. In recent years, cannabinoids such as delta-8-THC, delta -10-THC, tetrahydrocannabinolic acid (THCA), Δ9-tetrahydrocannabivarin (THCV), tetrahydrocannabiphorol (THC-P), and others have gained popularity within U.S. society.

Terminology and Pharmacology

Synthetic cannabinoid receptor agonists (SCRAs) refer to compounds that act on cannabinoid receptors but are structurally distinct from THC. These are sometimes called "non-classical cannabinoids." This category includes the substances originally found within K-2 and Spice. Endocannabinoids are endogenous cannabinoids, *phytocannabinoids* are derived from plants, and "semi-synthetic" cannabinoids are derived from or structurally related to phytocannabinoids or THC (as compared to SCRAs). Some experts recommend the term, "derived psychoactive cannabis products." The emergence and popularization of semi-synthetic cannabinoids and phytocannabinoids will be the primary focus of this discussion.

Cannabinoids are compounds that bind to cannabinoid receptors. Clinically relevant receptors include CB1 and CB2 which are typically classified as central and peripheral, respectively. Activity at the CB1 receptor accounts for the psychoactive effects of cannabinoids, as well as the concerning adverse effects. The pharmacologic activities of cannabinoids are complex, and often involve partial agonism, inverse agonism, varying agonism, or antagonism depending on concentration. The literature has conflicting reports, and there is still much to be discerned regarding many of the substances being found on the market. Potency is difficult to assess given the various

Continued next page

pharmacologic activities of cannabinoids and the lack of human clinical trials, but it has been reported that THC-P and THC-O are considered more potent than delta-9 THC, while TCHV, delta-8-THC, delta-10-THC, and CBN (cannabinol), are less potent.

Specific Substances

Cannabidiol or CBD is a naturally occurring cannabinoid that does not demonstrate psychoactive activity. Although it is non-intoxicating, many of the other cannabinoids derived from it are, and there is risk of contamination of CBD products, which has resulted in positive drug screening.

CBN acts at both CB1 and CB2 receptors, but has higher affinity for CB2. Its weak interaction with CB1 generally leads to a less potent psychoactive effect.

Delta-8-THC is structurally similar to delta-9-THC, and acts as a partial agonist to CB1 similar to delta-9-THC but with lower activity, resulting in less potent psychoactive effects. Delta-8-THC is banned in Virginia.

Delta-10-THC is less potent than delta-9-THC, exhibiting mild psychoactive effects. Clinical evidence on its physiological impact is limited.

THCA is non-psychoactive in its raw form but converts to psychoactive delta-9-THC when heated (via decarboxylation). THCA is advocated for purported anti-inflammatory and neuroprotective properties.

Hexahydrocannabinol or HHC is a semi-synthetic cannabinoid created through cyclization and hydrogenation of CBD. Production of HHC results in epimers and commercial products typically have a combination of the S and R epimers with a ratio that varies. The R epimer has binding activity similar to delta-9 at CB1 and CB2 receptors. The S epimer has less binding activity.

Delta-9-tetrahydrocannabivarin or THCV is a naturally occurring cannabinoid that acts as a CB1 antagonist at low doses and agonist at high doses. Generally considered less potent than delta-9 THC at the doses studied.

THC-O acetate or THC-O is not a naturally occurring cannabinoid but is structurally related. Its potency has been reported to be 2-3 times higher than delta-9-THC. THC-O has also been associated with vaping-associated lung injury, likely secondary to one of its heat-related metabolites.

Tetrahydrocannabiphorol or THC-P is a potent derivative that has higher affinity to CB1 receptors, reportedly 33 times more active than delta-9-THC. Due to its strong affinity, THC-P can lead to intense psychoactive effects and may pose a higher risk of adverse reactions, including anxiety, tachycardia, hallucinations, or sedation.

Clinical Effects

Perceived positive effects in the user may include relaxation, euphoria, or giddiness. Other adverse effects include xerostomia, nausea, vomiting, tachycardia, hypertension, anxiety or panic reactions, paranoia, agitation, hallucinations,

Continued next page

psychosis, sedation, and respiratory depression. While less potent derivatives such as delta-8 or delta-10 typically do not cause as many psychotropic effects, it is important to recognize that this is dose-dependent and any of these substances have the ability to cause significant or harmful effects. SCRAs have widely varied clinical effects and are more highly associated with adverse outcomes. Pediatric patients are more susceptible to the adverse effects of cannabinoids and warrant special attention.

Testing and Detection

Standard urine and blood tests for THC metabolites often detect delta-9-THC but may not consistently identify other derivatives, particularly synthetic cannabinoids. Advanced techniques such as *Gas chromatography–mass spectrometry* (*GC–MS*) or liquid chromatography–mass spectrometry (LC-MS) may be required for accurate identification, though these are not available in many hospitals and often not in a useful timeframe for clinical care.

Treatment

Management of cannabinoid toxicity involves supportive care. Mild symptoms (e.g., dizziness, dry mouth, drowsiness) are typically self-limiting. For severe cases (e.g., agitation, paranoia, or cardiovascular symptoms, renal dysfunction), treatment may involve benzodiazepines for agitation and/or intravenous fluids for hypotension. In cases with significant neurological or cardiovascular manifestations, patients require monitoring and treatments appropriate to the complications incurred. Patients may require prolonged observation to monitor and manage prolonged and potential delayed effects.

Conclusion

With the rise of cannabinoid derivatives, healthcare providers should be aware of varying potencies, psychoactive profiles, and potential adverse effects. Given their availability, healthcare providers should consider these compounds in differential diagnoses when encountering symptoms associated with cannabinoid toxicity. Testing capabilities are improving, but limitations remain; thus, clinical judgment is crucial in guiding patient care.

References available upon request