## K24 Preclinical Investigation of CP47,497: A Widely Abused Synthetic Cannabinoid

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The goal of this presentation is to educate attendees about CP47,497 (2-[(1R,3S)-3-Hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol), a synthetic cannabinoid recently banned by the DEA. The pharmacology of this compound was first described in the scientific literature in 1982, but prior to its ban was being sold for consumption primarily through internet sources or head shops and was associated with a large spike in emergency department visits. CP47,497 activates the cannabinoid receptor 1 ($CB_1R$) and dose-dependently elicits cannabimimetic effects that are more potent than effects produced from $\Delta^9$- tetrahydrocannabinol (THC). Importantly, these studies provide novel evidence using a whole animal model that the $CB_1R$ antagonist rimonabant reverses the potent cannabimimetic effects of CP47,497

This presentation will impact the forensic science community by providing a direct comparison of synthetic cannabinoid and THC behavioral data in whole animal studies.

CP47,497 and other synthetic cannabinoid compounds were originally synthesized as tools to investigate the mechanism by which marijuana affects the brain as well as for the development of potential therapeutic agents to treat pain and other disorders. However, studies addressing the behavioral consequences of synthetic cannabinoids are scant. Synthetic cannabinoids pose an enhanced risk for abuse, toxicity, and addiction due their increased potency and efficacy over THC. The goal of the present study was to determine whether the pharmacological effects of CP47,497 are achieved in a dose-dependent and time-dependent manner. Since CP47,497 binds to $CB_1$ receptors and elicits THC-like effects, it was investigated whether rimonabant would attenuate its pharmacological actions *in vivo*.

All mice received intraperitoneal injections of CP47,497, THC, or vehicle. To test for cannabimimetic subjective effects, a tetrad model was utilized that consisted of four outcome measures: catalepsy; antinociception (tail flick latency); hypothermia; and, locomotor activity. Although many pharmacological agents can produce one or a subset of these effects, drugs that activate $CB_1$ receptors produce measurable effects in all four parameters of the tetrad. Immediately following behavioral testing, mice were humanely euthanized and blood and tissue were harvested for CP47,497 quantification. Samples are currently being analyzed on an Applied Biosystems Liquid Chromatograph/Tandem Mass Spectrometer (LC/MS/MS) interface utilizing electrospray ionization and selective ion monitoring, using an acetonitrile liquid-liquid extraction procedure that the laboratory has previously developed validated methods for quantification of THC and other cannabinoids in blood and tissue.

In the cumulative dose-response experiment, mice were treated with THC (3, 10, 30, 100, and 200mg/kg), CP47, 497 (0.3, 1, 3, 10 and 30mg/kg), and vehicle control. Potency ratios for comparison of CP47,497 to THC were calculated including 95% confidence limits for each: catalepsy 7.49 (5.72 – 9.76), antinociception 9.11 (3.76 – 21.98), and hypothermia 7.68 (4.55 – 12.83), which clearly demonstrate CP47,497's enhanced potency and efficacy. In the final component of the tetrad, 30mg/kg CP47,497 produced a statistically significant increase in locomotor depressing effects versus control. Based on the data obtained from the dose-response study, 30mg/kg CP47,497 and 100mg/kg THC were used in subsequent antagonism studies. Both 30mg/kg CP47,497 and 100mg/kg THC produced statistically significant increases in catalepsy, hypothermia, antinociception, and a decrease in locomotor activity versus control. CP47,497 and THC-induced catalepsy and hypothermia were reversed by pretreatment with 3mg/kg rimonabant. Although 3mg/kg rimonabant antagonized the antinociceptive effects of 100mg/kg THC, 10mg/kg rimonabant was required to block the antinociceptive and locomotor depressing effects of 30mg/kg CP47,497.

This study's results provide the first *in vivo* evidence that the cannabimimetic effects of CP47,497 are $CB_1$ mediated as blockade of these effects is achieved with the $CB_1$ antagonist, rimonabant. Given that CP47,497 elicits dose-dependent cannabimimetic effects that are markedly (7 – 9 times) more potent than THC-containing substances, these data are consistent with the large number of abusers of this compound presenting with severe cannabis-related adverse effects that require emergency department interventions.

**CP47,497, Spice, THC**

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