Marijuana Effect on Differentiating an Opioid from Placebo During the Discrimination Phase of a Human Abuse Potential Study

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Background

Human abuse potential (HAP) studies are conducted to measure the potential abuse of a drug with rewarding properties. Subject selection is important for insuring subjects have the ability to detect liking with the drug under investigation.

In adherence to the U.S. FDA draft guidance,[1] subjects recruited for such trials have used opioids recreationally, but are not physical dependent on them. These subjects are then required to demonstrate they can discriminate between active test opioid and placebo. A positive urine drug tests (UDT) for illicit substances serve as a routine exclusion for study participation to eliminate potential bias or risk of pharmacodynamic carryover in the discrimination test. However, many subjects recruited for opioid HAP studies use marijuana, and the plant's active compound, tetrahydrocannabinol (THC), is often exempt from this exclusion, in part to improve recruitment and retention of subjects.

The impact of THC on pharmacodynamic assessments in drug discrimination is typically considered insignificant but is not well characterized or understood. There is some evidence that THC might affect discriminatory responses.[2] Some studies suggest a neurobiological link between the endogenous opioid and cannabinoid systems on both neuroreceptor and behavioral levels, exerting common effects through activation of dopaminergic "reward" pathways.[3,4] Researchers in neurology view the endogenous opioid and cannabinoid systems as independent, yet parallel and overlapping, with THC influencing dopamine discharge by triggering the release of endogenous opioids in the brain[5,6] at mu-opioid receptors.[7]

Methods

In 64 subjects in a single HAP study, investigators examined the potential influence of THC, including quantitative levels where applicable, on ability to discriminate between 20 mg of intranasal oxycodone and placebo. Quantitative and qualitative UDTs were used as surrogate assessments for CNS receptor exposure to THC. Subjects were assigned to positive or negative THC status based on qualitative UDT at check-in conducted at least 12 hours prior to the first dose of drug discrimination.

The standard for ability to discriminate was defined as a minimum E_{max} for drug liking (eg, ≥65 mm), a minimum E_{max} separation from placebo (eg, ≥15 mm difference), and an appropriate placebo response as measured through a bipolar VAS (eg, 40 – 60 mm). Subjects who did not complete drug discrimination or who completed but were terminated from the study for reasons other than failing to properly discriminate between active and placebo (eg, emesis, withdrawn consent) were excluded from this analysis.

Eligible subjects were healthy men and women aged 18 to 55 years old at the time of screening and engaged in recreational opioid use without opioid dependency, as determined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition 13.

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Objectives

This study was conducted to assess whether subjects testing positive for THC would be able to discriminate an opioid from placebo during the discrimination phase and, if there is any statistical significant impact on drug discrimination.

Results

Of the 64 subjects enrolled, 31 (48%) were positive for THC prior to drug discrimination (Figure 1).

Ten subjects (6 of which positive for THC) did not complete drug discrimination and were excluded from analysis due to:

- Emesis (5 Subjects)
- Withdrawn consent (3 Subjects)
- Inability to complete study meal (2 Subjects)

The remaining 54 patients (Figure 2)completed drug discrimination:

- Passed and were randomized to treatment (39 Subjects)
- Positive UDT rate for THC was 48.7%
- Mean urine carboxy-THC concentrations of 705 ng/mL

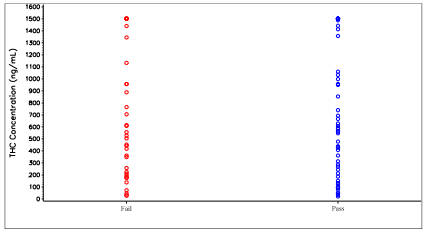

Figure 2: Distribution of Individual THC Results by Pass/Fail (n=54)

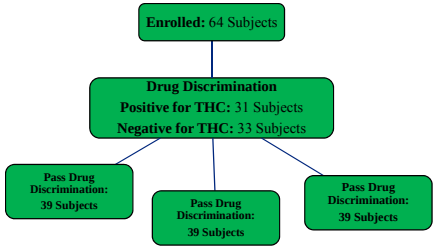

Figure 1: Subject Disposition

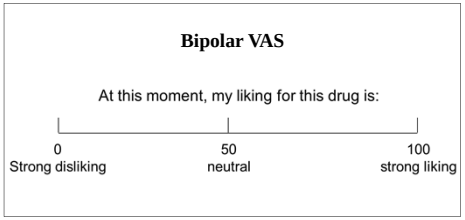

Figure 3: Measurement Of Subjective PD Effects: Visual Analog Scale

A total of 15 subjects did not successfully discriminate.

- Positive urine drug screen rate for THC was 40%
- Mean urine carboxy-THC concentrations of 417 ng/mL

Discriminators and non-discriminators did not have a statistically significant difference in positive UDT rates (p=0.5650) and mean urine carboxy-THC concentrations (p=0.2797).

Discussion

After smoking, maximum THC concentration in the brain is reached within 15 minutes, coinciding with the onset of peak psychological and physiological effects. Psychological effects then reach a plateau that can persist 2 to 4 hours before declining slowly following acute exposure.[2] THC, as with other plant cannabinoids, is extremely lipid soluble, accumulating in fatty tissues and reaching peak concentration in 4-5 days. The tissue half-life of THC is ≈7 days, but complete elimination may take up to 30 days.[3]

In trial subjects sequestered and observed overnight, and therefore THC abstinent for 12 or more hours, significant mental impairment or confounding pharmacodynamics effects from prior cannabis use would not be expected. Any potential central nervous system (CNS) changes or neuroplastic changes from chronic exposure have been poorly characterized to date. These data appear to corroborate the lack of lingering pharmacodynamics effects from THC use as determined by medical investigators evaluating the abuse potential of drugs in recreational drug using populations. While these data do not refute any putative interaction between the cannabinoid and opioidergic systems, it appears that any effects do not impact drug liking discrimination in opioid versus placebo HAL studies

The presence or absence of a positive UDT for THC at least 12 hours prior to dosing did not influence the ability of subjects in this sample to successfully discriminate between an opioid control versus placebo. Quantitative THC levels in 64 subjects do not accurately predict the ability of a subject to pass or fail an opioid drug discrimination test when evaluated. There where no differences between hydrocodone and oxycodone when evaluated. The extent and duration of THC use was not included in this analysis but could be an important factor in further research. Inclusion of THC positive subjects in opioid HAP studies is unlikely to impact pharmacodynamics assessments and ultimately improves the external validity of study results.

Conclusion

Successful opioid discriminators were associated with a higher positive THC drug screen rate and mean carboxy-THC urine concentrations when compared to non-discriminators, but differences were not statistically significant. The objective measurements of THC did not correlate with subjects' ability to discriminate between active drug and placebo in this intranasal opioid HAL study.

Detectable exposure to THC did not affect whether an individual passed or failed the discrimination phase. This means that it may not be necessary to exclude recent users of marijuana from opioid HAP studies. Further research is necessary to fully elucidate the influence of THC in HAP studies.

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