Investigation of the Reinforcing and Discriminative Properties of Plant-Derived, Highly Purified Cannabidiol (CBD) in Rats and Monkeys

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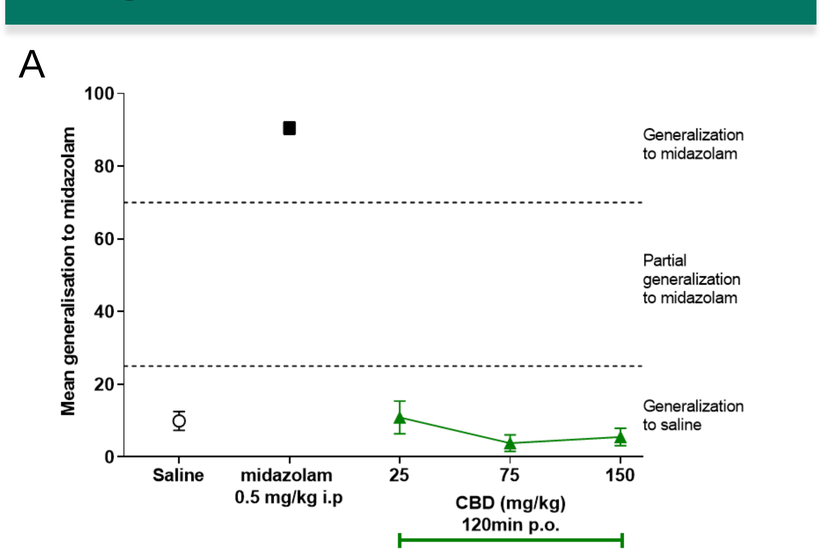
SUMMARY

- Plant-derived, highly purified CBD (Epidiolex® 100 mg/mL oral solution) is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥2 years of age.
- Studies were conducted in accordance with FDA Guidance (Assessment of Abuse Potential of Drugs (2017)) in support of NDA application and represent a component of the 8-factor analysis (8FA) for determination of drug scheduling in the USA.
- Accordingly, the discriminative properties of CBD were assessed in rats trained to midazolam and reinforcing properties were assessed using the *i.v.* self-administration procedure in rats trained to heroin and rhesus monkeys trained to midazolam.
- CBD, at doses that produced systemic exposure equal to and greater than those observed in humans, was not a strong positive enforcer and did not produce an interoceptive effect similar to midazolam.
- These data contributed to the 8FA for Epidiolex (a specific formulation of plant-derived, highly purified CBD) and its Schedule V Controlled Drug classification in the USA.
- These data strongly suggest that CBD possesses negligible potential for human abuse.

RESULTS

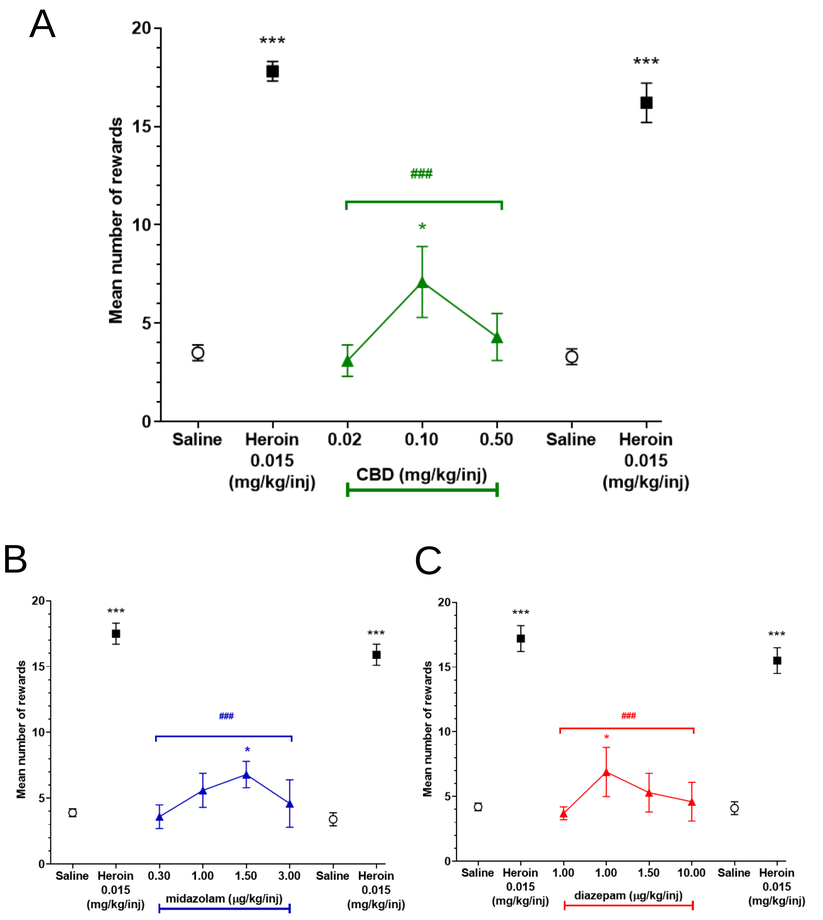
Drug discrimination in midazolam-trained rat



Effects of orally administered (A) CBD; (n=6), (B) midazolam (n=6-8) and (C) alprazolam (n=6-13) in rats trained to discriminate midazolam (0.5 mg/kg i.p.) from saline determined 120 min (CBD) or 30min (midazolam & alprazolam) after dosing. Data shown as mean % generalisation to midazolam ± SEM. Saline and midazolam (0.5 mg/kg i.p.) data represent the mean of the four test sessions preceding the first oral dose of test compound.

- In midazolam-cued drug-discrimination, all orally administered CBD doses (20, 75, 150 mg/kg) generalized to the saline cue (Fig A).
- Orally administered midazolam (Fig. B) and alprazolam (Fig. C) dose-dependently generalised to the discriminative cue elicited by intraperitoneally injected midazolam (0.5 mg/kg).

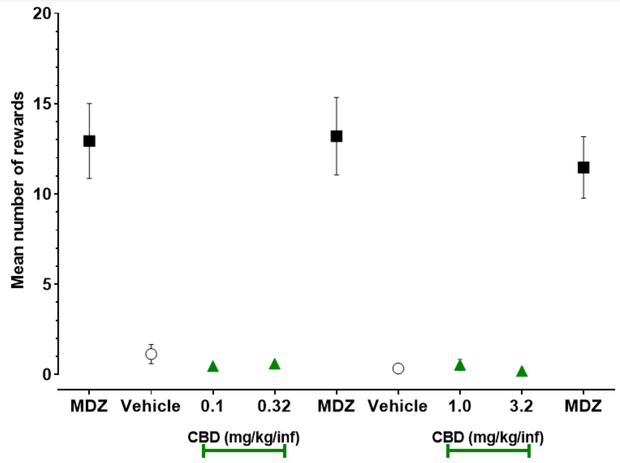
Evaluation of reinforcing effects of CBD in the heroin-trained rat



Effect of CBD (A) midazolam (B) and diazepam (C) in the heroin trained rat. Data are represented as the mean ± SEM number of injections per session during the last three sessions for each condition in rats responding under an FR3 schedule of *i.v.* self-administration. Means are back-transformed and adjusted for differences between animals. SEM are calculated from the residuals of the statistical model. Cannabidiol was compared to saline and heroin and family-wise error determined by Dunnett's test. Heroin was compared to saline by the multiple t test. Significantly different to saline *p<0.05, ***p<0.001. Significantly different to heroin ###P<0.001.

- Heroin maintained self-administration in rats at levels significantly greater than saline (17.6 ± 0.5 infusions/session, n = 39 vs 3.7 ± 0.2 infusions/session, n = 39; p<0.001).
- CBD (at 100 but not 10 or 300 µg/kg/infusion), maintained a low level of self-administration [6.9±1.8 infusions/session; n=8] at a level that was significantly greater than saline (p<0.05).
- The reference comparators, diazepam (1µg/kg/infusion) [7.0±2.1 infusions/session; n=8] and midazolam (1.5µg/kg/infusion) [7.3±1.3infusions/session; n=16] maintained significantly greater self-administration than saline (p<0.05), and met the criteria for weak positive reinforcers.

Evaluation of reinforcing effects of CBD in the midazolam-trained monkey



Data are represented as the mean ± SEM number of number of infusions received in the last three sessions of each condition; n=5. MDZ = midazolam. SEM for number of rewards in response to CBD and vehicle groups smaller than symbols.

- Monkeys received a mean of 12.9 ± 2.1 infusions per session of midazolam and 1.1 ± 0.5 infusions per session of vehicle.
- Responding for CBD was not statistically different from vehicle, with the maximum number of infusions received per session varying from 0.2 ± 0.1 (3.2 mg/kg/infusion) to 0.60 ± 0.30 (0.32 mg/kg/infusion).
- When each of the three largest doses of CBD was given as a bolus *i.v.* injection, plasma C_{max} values were 478 ± 66, 1730 ± 173, and 5530 ± 421 ng/ml; these values were between 1.5 and 12-fold higher than those obtained in humans receiving CBD therapeutically.

METHODS

- Reinforcing effects of CBD were examined in ♂ and ♀ midazolam-trained monkeys self-administering 0.010 (n=3) or 0.032 (n=2) mg/kg/infusion of midazolam (*i.v.)* under a fixed-ratio schedule (FR30). When responding for midazolam was stable, midazolam was replaced with CBD vehicle (1:1:9 ethanol:emulphor:saline) or CBD (0.1, 0.32, 1.0, and 3.2 mg/kg/infusion *i.v.*). Vehicle and each dose of CBD was examined for ≥ four sessions until responding was stable.
- The reinforcing effects of CBD were also examined in ♂ heroin-trained Sprague-Dawley rats. Rats trained to stably self-administer heroin (15 µg/kg/inj.) on a fixed-ratio schedule (FR3) of reinforcement in 2-hr training sessions, underwent saline extinction followed by assessment of the reinforcing effects of CBD (20, 100, 500 µg/kg/infusion), diazepam (1, 3, 4.5 or 10 µg/kg/infusion), and midazolam (0.3, 1, 1.5, 2.25 or 3 µg/kg/infusion).
- The discriminative properties of CBD were evaluated in ♀ Lister hooded rats, trained to discriminate midazolam (0.5mg/kg *i.p.*) from saline in a 2-choice operant test. Lever-pressing was reinforced by sweetened milk rewards on a FR5 schedule. Having reached >75% correct responding for midazolam versus saline, CBD (20, 75, 150 mg/kg *p.o.*), midazolam (0.5, 1.0, 1.5 mg/kg *p.o.*), and alprazolam (0.125, 0.25, 0.5, 1.0 mg/kg *p.o.*) were examined.
- HPLC/MS/MS of plasma CBD exposure was performed for assessment of plasma [CBD].

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