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A cannabis extract and morphine: increased analgesia without increased respiratory depression

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Introduction: Δ^9-Tetrahydrocannabinol (THC), a major psychoactive component of cannabis, enhances the thermal analgesic properties of morphine[1]. Studies have also shown possible potentiated effects of THC using combinations of different cannabinoids[2]. Therefore, we aimed to study the thermal analgesic properties and respiratory effects of cannabis extract in combination with morphine.

Methods: Cannabis extract was prepared from cannabis flowers using hexane liquid-liquid extraction in vehicle (18:1:1 saline: ethanol: ethoxylated castor oil). The cannabinoid content was quantified using HPLC. Morphine was dissolved in saline. Adult female CD1 mice (25-30 g) were randomly assigned to treatment groups. Animals were injected intravenously with extract (0-0.8 mg/kg THC; n = 5/group), morphine (0.2-12 mg/kg; n = 8), extract (0-0.8 mg/kg THC) and 6 mg/kg morphine (n = 8), or saline (n = 8). Mice were habituated to their environment for 60 min prior to pre- and post-treatment tests. Thermal stimulus response was measured using a ramped hotplate[3] with a temperature range of 32.1℃ to 52.1℃. Withdrawal latencies were measured at 5 min after treatment. Mice were then placed in modified Falcon tubes and videotaped for 10 min. Respiratory rate (min^{-1}) was measured during the 9-10th min interval (19-20 minutes after treatment). ANOVA or Kurskal-Wallis followed by Dunnett's or Dunn's multiple comparison test was performed ($\alpha = 0.01$) as appropriate. Delta latencies were calculated by subtracting pre-treatment from post-treatment latencies. Data are shown as mean with SD.

Results: Extract did not affect withdrawal latency or respiratory rate at any dose tested ($P > 0.01$ compared to vehicle). Compared to saline, morphine increased latency at 6 and 12 mg/kg (-0.4±6.7 s vs. 36.8±18.3, 60.4±19.3 s; P = 0.0009, <0.0001) and decreased respiratory rate at 1-12 mg/kg (186±19 min^{-1} vs. 147±15, 125±17, 125±17 min^{-1}; P = 0.0063, 0.0001, 0.0001). Significant increases in delta latency were seen between 6 mg/kg morphine with vehicle, and combinations of 0.2, 0.4, and 0.8 mg/kg extract and 6 mg/kg morphine (20.0±8.9 s vs. 54.8.8±21.5, 66.8±8.6, 64.9±13.3 s; P = 0.0005, 0.0001, 0.0001) without increased respiratory depression (132±15 min^{-1} vs. 122±16, 111±13, 119±24 min^{-1}; P= 0.77, 0.16, 0.59).

Conclusion: Non-analgesic doses of a cannabis extract combined with a fixed dose of morphine produced an increase in thermal analgesia without added respiratory depression.

References:

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2. Karniol IG and Carlini EA (1973). *Psychopharmacologia* **33(1):** 53
3. Hunskaar S *et al.* (1986). *Behav Brain Res* **21(2)**: 101