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Investigating the Cardiopulmonary and Antinociceptive Effects of Fentanyl, Xylazine, and their Mixture in Male Rats

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Cases of fatal opioid overdose and opioid use disorder have drastically increased in the past decade. One key contributor to this epidemic is the increase in heterologous drug mixtures consisting of different opioids (e.g., heroine, fentanyl) with non-opioids. Recently, xylazine has infiltrated the drug supply market, prompting the United States Office of National Drug Control Policy to declare mixtures of xylazine and fentanyl an emerging threat to the United States. Despite the exponential increase in use of xylazine and fentanyl mixture, interactions between these drugs in the context of overdose and substance use disorder are not well-characterized. To better understand both the physiological effects of xylazine and nature of the interactions between xylazine and fentanyl, this study investigated the cardiopulmonary and antinociceptive effects of xylazine and fentanyl alone, and in a mixture in rats. Male Sprague Dawley rats were administered subcutaneous xylazine (0.1 mg/kg – 10 mg/kg) or fentanyl (0.01 mg/kg – 0.32 mg/kg). Heart rate, breath rate, oxygen saturation, and thermal antinociceptive effects were measured every 10-minutes for 2 hours. Subsequently, mixtures of xylazine and fentanyl were administered to investigate the nature of the interactions with regard to cardiopulmonary and antinociceptive effects. Fentanyl produced significant dose-dependent decreases in heart rate, oxygen saturation, and thermal nociception, lasting approximately 50 minutes prior to returning to baseline. Xylazine produced significant dose-dependent reduction in heart rate and breath rate but was without effect on oxygen saturation and thermal nociception. Bradycardia and reductions in breath rate persisted for at least 2 hours post xylazine administration. Preliminary interactions between xylazine and fentanyl were largely additive in nature, with individual differences observed. These data demonstrate the cardiopulmonary and antinociceptive effects of xylazine and fentanyl, contributing to growing body of literature describing the abuse-related effects of these drugs. Future studies will determine the presence of pharmacokinetics interactions between xylazine and fentanyl, as well as develop and evaluate candidate therapeutics to help treating users of these drug mixtures with the goal of preventing lethality due to drug overdose.