Veterinary anesthetic xylazine produces synergistic antinociceptive effects with the opioid fentanyl in mice

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A recent twist to the ongoing tragedy of the opioid epidemic is the combination of fentanyl with the veterinary tranquilizer xylazine known on the street as “tranq dope.” Xylazine is an α2 adrenoceptor agonist used for sedation in large animals. In Philadelphia and other major cities, illicit bags of fentanyl are increasingly adulterated with xylazine significantly adding further insult to current toxicity of the opioid crisis. One key pharmacological feature of xylazine may be the potential to increase the duration of action, or high, of fentanyl which has a notoriously shorter half-life than other abused opioids. In addition, we hypothesize that xylazine potentiates the pharmacological effects of fentanyl through opioid and norepinephrine synergistic mechanisms. To examine this hypothesis, Swiss-Webster mice were tested for their baseline sensitivity to a 52.5°C hot-plate as measured by a hind-paw lick or jump with a 60 sec cut-off period. After baseline measures, mice were injected (IP) with either fentanyl alone, xylazine alone, or combinations of fentanyl and xylazine in ratios of 1:1, 1:3 and 3:1 fentanyl to xylazine. After a 10 min pretreatment, mice were tested again on the hot plate. Both fentanyl and xylazine produced full, dose-dependent increases in antinociception although fentanyl was 10-fold more potent than xylazine at doses without motoric effects. When combined, simple additivity was observed with the 3:1 ratio of fentanyl to xylazine. However, synergistic effects were observed for the ratios of 1:1 and 1:3 fentanyl to xylazine. In conclusion, when combining fentanyl and xylazine in a 1:1 and 1:3 ratios, xylazine augments the pharmacological effects of fentanyl if the xylazine administered is equal to or greater than the relative potency of fentanyl. This augmentation may help to explain the recent trend to combine these two agents for illicit sale despite the increasing toxicity. The underlying mechanisms of this synergism will be investigated further through opioid and norepinephrine competitive antagonism and time-course studies.

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