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The Lack of Contribution of 7-Hydroxymitragynine to the Antinociceptive Effects of Mitragynine in Mice: A Pharmacokinetic and Pharmacodynamic Study

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Abstract

Kratom (*Mitragyna speciosa*), a Southeast Asian tree, has been used for centuries in pain relief and mitigation of opium withdrawal symptoms. Mitragynine (MTG), the major kratom alkaloid, is being investigated for its potential to provide analgesia without the deleterious effects associated with typical opioids. Concerns have been raised regarding the active metabolite of MTG, 7-hydroxymitragynine (7HMG), which has higher affinity and efficacy at μ-opioid receptors than MTG. Here we investigated the hotplate antinociception, pharmacokinetics, and tissue distribution of MTG and 7HMG at equianalgesic oral doses in male and female C57BL/6 mice to determine the extent to which 7HMG metabolized from MTG accounts for the antinociceptive effects of MTG and investigate any sex differences. The mechanism of action was examined by performing studies with the opioid receptor antagonist naltrexone. A population pharmacokinetic/pharmacodynamic model was developed to predict the behavioral effects after administration of various doses of MTG and 7HMG. When administered alone, 7HMG was 2.8-fold more potent than MTG to produce antinociception. At equivalent effective doses of MTG and 7HMG, there was a marked difference in the maximum brain concentration of 7HMG achieved, i.e., 11-fold lower as a metabolite of MTG. The brain concentration of 7HMG observed 4 hours post administration, producing an analgesic effect <10%, was still 1.5-fold higher than the maximum concentration of 7HMG as a metabolite of MTG. These results provide strong evidence that 7HMG has a negligible role in the antinociceptive effects of MTG in mice. SIGNIFICANCE STATEMENT: Mitragynine (MTG) is being investigated for its potential to aid in pain relief, opioid withdrawal syndrome, and opioid use disorder. The active metabolite of MTG, 7-hydroxymitragynine (7HMG), has been shown to have abuse potential and has been implicated in the opioid-like analgesic effect after MTG administration. The results of this study suggest a lack of involvement of 7HMG in the antinociceptive effects of MTG in mice.

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