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## The median effective dose of ketamine and gabapentin in opioid-induced hyperalgesia in rats: an isobolographic analysis of their interaction.

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### Abstract

**BACKGROUND:** Ketamine and gabapentin have been shown to prevent the delayed hyperalgesia induced by short-term use of systemic opioids. The mechanism of this action is believed to be likely at the spinal level, through an antagonism of the N-methyl-D-aspartate receptors for ketamine, and through a specific binding site for gabapentin. In this study, we sought to determine the nature of the interaction of these 2 mechanistically distinct antihyperalgesic drugs in a model of opioid-induced hyperalgesia in rats. The median effective antihyperalgesic doses of each drug and of their combination were first defined, to assess the nature of the interaction using an isobolographic analysis.

**METHODS:** Long-lasting hyperalgesia was induced in male Sprague Dawley rats with subcutaneous fentanyl (4 injections, 60 µg/kg per injection at 15-minute intervals) resulting in a total dose of 240 µg/kg. Subcutaneous ketamine, or intraperitoneal gabapentin, or their combination was administered 30 minutes before the first subcutaneous fentanyl injection. Sensitivity to nociceptive stimuli (von Frey filaments) was assessed on the day of the experiment and on the day after injections. The dose of ketamine and gabapentin received by a particular animal was determined by the response of the previous animal of the same group, using an up-and-down technique. Initial doses were 10 mg/kg and 300 mg/kg, with dose adjustment intervals of 1 mg/kg and 30 mg/kg, in the ketamine and gabapentin groups, respectively. The initial doses of ketamine and gabapentin were 5 mg/kg and 150 mg/kg, respectively, in the ketamine-gabapentin group, with the same dose adjustment intervals. Antihyperalgesic efficacy was defined as complete prevention of hyperalgesia on the day after drug injections.

**RESULTS:** The median effective antihyperalgesic doses (median value and 95% confidence interval) of ketamine and gabapentin were 12.4 mg/kg (11.7-13.1 mg/kg) and 296.3 mg/kg (283.5-309.1 mg/kg), respectively. The median effective antihyperalgesic dose of the combination was 4.3 mg/kg (3.7-4.6 mg/kg) for ketamine and 123.9 mg/kg (111.1-136.7 mg/kg) for gabapentin.

**CONCLUSION:** The isobolographic analysis demonstrated that the combination of the 2 drugs produces effective antihyperalgesia with a supraadditive (synergistic) action.

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