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Synergism between dexketoprofen and meloxicam in an orofacial formalin test was not modified by opioid antagonists

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Abstract:
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs for the management of acute and chronic pain. The role of the opioid system in the synergism between NSAIDs is not well characterized. Mice were injected with a 5% formalin solution (20 μl) into the upper right lip to perform an orofacial formalin test. The isobolographic method was used to determine the interaction between dexketoprofen, which is the (S)-(+) enantiomer of ketoprofen, and meloxicam co-administration. Additionally, the non-selective, opioid antagonist naltrexone, the selective δ opioid receptor (DOP) antagonist naltrindole and the selective κ opioid receptor (KOP) antagonist norbinaltorphimine were used to assess the opioid effects on this interaction. Intraperitoneal administration of dexketoprofen or meloxicam induced dose-dependent antinociception with different phase I and phase II potencies in the orofacial formalin test. Meloxicam displayed similar potencies (ED_{50}) in phase I (7.20 mg/kg) and phase II (8.60 mg/kg). Dexketoprofen was more potent in phase I (19.96 mg/kg) than in phase II (50.90 mg/kg). The interactions between dexketoprofen and meloxicam were synergistic in both phases. This was determined based on the fixed ratios (1:1) of their ED_{50} values, which were determined by isobolographic analysis. Furthermore, this antinociceptive activity does not seem to be modulated by opioid receptor blockers because they did not induce changes in the nature of this interaction. This finding may be relevant with regards to NSAID multi-modal analgesia where an opioid antagonist must be used.

Key words:
algesiometric tests, antinociception, isobolographic analysis, synergism