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Effect of clonidine and ketotifen on tolerance induced to morphine antinociception in mice

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Background and Aims: Recently it has been demonstrated that histamine can modulate currents gated by the glutamate NMDA receptor. NMDA receptors antagonists alleviate many of the symptoms of opioid withdrawal and decrease tolerance induced to morphine antinociception. On the other hand, the adrenergic receptors are in challenging with morphine tolerance. Ketotifen is an antihistamine agent and clonidine is an alpha agonist. The aim of this study was to investigate the effect of ketotifen and clonidine on tolerance induced to morphine antinociception in mice.
Methods: In the present study different groups of mices were received morphine (30 mg/kg, ip) ,morphine (30 mg/kg, ip) +ketotifen (4,8,16 mg/Kg, ip), morphine (30 mg/kg, ip) +clonidine (0.1, 0.2 mg/kg, ip) and morphine (30 mg/kg, ip) + clonidine (0.1mg/kg, ip) + ketotifen (4mg/Kg, ip) once a day for four days. Tolerance was assessed by administration of morphine (9 mg/kg, ip) on fifth day and tested by HOT PLAT test. The licking of hand was a marker to determine the latency time of morphine analgesia.
Results: This study shows that pretreatment of animals with a single doses of ketotifen (8 and 16 mg/kg, ip), clonidine (0.2mg/kg, ip) and ketotifen + clonidine 30 min prior to receiving morphine (30mg/kg, ip) during the development of tolerance to the morphine on days 1-4 of morphine administration, caused a significant ($p < 0.001$) effect on tolerance induced to morphine antinociception in mice.
Conclusions: These finding represent the advantage of co-administration of ketotifen (8 and 16 mg/kg, ip) and clonidine (0.2 mg/kg, ip) or ketotifen (4mg/kg, ip) and clonidine (0.1 mg/kg, ip) with morphine in complication due to tolerance induce to morphine antinociception in mice. These results suggested that the receptors (H1) and α2 is important in tolerance induced to morphine antinociception.

Keywords: Clonidine; Ketotifen; Morphine; Tolerance