Evaluation of Methadone and Magnesium Sulfate Administration on Morphine-induced Tolerance and Dependence

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Abstract: Due to the increasing use of opioid analgesics for pain management regardless of their contingent risk of tolerance occurrence, it is essential to find solutions to reduce the phenomenon of tolerance to the analgesic effects of these drugs.

In this study the probable preventive effect of methadone and magnesium sulfate in tolerance and dependence occurrence is evaluated in mice.

The animals divided randomly in 6 groups and received the drugs intraperitoneal as this protocol once a day for 4 days:
A. saline (10 ml/kg), B. saline (10 ml/kg) + morphine (30 mg/kg), C. saline (10 ml/kg) + methadone (0.5 mg/kg), D. saline (10 ml/kg) + morphine (30 mg/kg) + methadone (0.5, 1 and 1.5 mg/kg), E. saline (10 ml/kg) + morphine (30 mg/kg) + magnesium sulfate (20, 40 and 60 mg/kg), F. saline (10 ml/kg) + morphine (30 mg/kg) + methadone (0.5 mg/kg) + magnesium sulfate (20 mg/kg)

Tolerance was assessed by administration of morphine (9 mg/kg), 24 hours after the last dose of morphine (fifth day) and the analgesic effect of morphine in all groups was measured using a hot plate. To evaluation of the dependency rate, 2 hours after the last dose of morphine on the fourth day, naloxone (5 mg/kg) is injected and the withdrawal symptoms were assessed.

It is found that pretreatment with methadone or magnesium sulfate decreased the degree of tolerance and dependence but in co-administration of methadone and magnesium sulfate before morphine administration, contradictory results exacerbated.

From acquired results, it can be concluded that methadone and magnesium sulfate alone could prevent the development of dependence and tolerance to the analgesic effects of morphine which can be related to NMDA receptor antagonist and calcium channel blocking effect of methadone and magnesium sulfate.

Keyword: Methadone; Magnesium Sulfate; Morphine; Tolerance; Dependency