Effects of chronic administration of calcium magnesium soft gels (CalMag) on morphine tolerance and dependence in mice

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Chronic use of opioids such as morphine in treatment of pain is limited by development of tolerance and dependence (Achiller, 2005). In previous study we showed that acute administration of calcium magnesium soft gel (CalMag) attenuated morphine tolerance and withdrawal syndrome (Rabbani et al., 2006). The aim of the present study was to evaluate the effect of chronic administration of CalMag on development of morphine tolerance and dependence in mice.

Male NMRI mice (n=6-8/group; 25-30g; Pasture Institute, Iran) were made tolerant (twice daily sc injection of 20 mg kg⁻¹ of morphine for 4 days) and dependent (twice daily sc injection of increasing dose of morphine for 5 days) to morphine. CalMag soft gel was injected ip 30 min prior to morning injection of morphine. Naloxone (5 mg kg⁻¹, ip) challenge was made two hours after the last injection of morphine and the signs of withdrawal were recorded. Tolerance was assessed based on loss of antinociceptive effect of morphine, using the tail-pinch test 30 min after final morphine injection. Statistical analysis was performed using one-way ANOVA with an appropriate post-hoc test. In all comparisons, P<0.05 was considered significant. Data expressed as mean ± S.E.M.

In morphine tolerant mice, chronic administration of CalMag at 50/25, 25/12.5, 12.5/6.25 (Ca/Mg ratio) mg kg⁻¹, significantly increased the response time to pain from control value of 1.9 s (± 0.4) to 12.8 s (± 1.6), 12.7 s (± 1.1) and 10.3 s (± 1.6), respectively. Chronic administration of CalMag at 50/25 and 25/12.5 (Ca/Mg ratio) mg kg⁻¹, significantly decreased the number of jumps from 62.5 (± 13.3) and 72.0 (± 9.8) to 25.9 (± 4.8) and 19.7 (± 4.9), respectively.

The effects of CalMag in alleviating withdrawal signs and preventing tolerance could not be due to the other contents of the capsules as administration of Ca and Mg also blocked the tolerance and dependence. Since these capsules are used as nutritional supplement, and so far no undesirable effects have been reported in humans, further studies could be designed to evaluate their effects in human morphine addicts.