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Evaluation of the systemic oxidative stress status upon *in vivo* exposure to tramadol and tapentadol

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Abstract

Background: Tramadol and tapentadol are synthetic centrally acting analgesic opioids, used in the treatment of moderate to severe pain [1]. Despite their optimized therapeutic and safety profiles, these compounds are associated with adverse effects, namely CNS and respiratory depression, abuse and dependence [2, 3]. Oxidative stress is one of the main toxicity mechanisms triggered by opioids [1, 4, 5]. **Objective:** The aim of this study was to evaluate putative systemic oxidative stress changes induced by a therapeutic dose of tramadol and tapentadol. **Methods:** Three groups of Wistar rats (9 animals each) were administered intraperitoneally with 50 mg/kg tramadol/tapentadol during 8 alternate days, while the control group was treated with saline solution [1]. Serum total antioxidant capacity and ROS/RNS levels were determined through spectrophotometry, whilst serum cysteine and homocysteine levels were quantified through ELISA, with commercial kits, according to the manufacturers' instructions. Statistical data analysis was performed through an Analysis of Variance (ANOVA), followed by Dunnett's multiple comparison's test. **Results:** An increase in ROS/RNS levels was observed in tramadol (*p<0.05) and tapentadol (***p<0.001) groups. However, regarding the antioxidant concentration, no significant differences were found. A statistically significant decrease in the concentration of cysteine was observed in the tramadol-administered group (*p<0.05). Furthermore, a statistically significant increase in the concentration of homocysteine was evident in the tapentadol-administered group (*p<0.05). **Conclusions:** The increase in ROS/RNS levels demonstrates that tramadol and tapentadol cause oxidative stress, with no changes in the total antioxidant capacity. However, as cysteine may have an antioxidant effect, the decrease in its serum levels may indicate that tramadol affects the levels of adjuvant antioxidants [6]. Since high levels of homocysteine causes oxidative stress, the increase in its serum concentration indicates that tapentadol induces oxidative stress [7]. In conclusion, tramadol and tapentadol must have a controlled prescription given their potential oxidative toxicity.

Keywords: tramadol; tapentadol; oxidative stress; cysteine; homocysteine

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