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ORIGINAL ARTICLE

# Effect of tramadol on metamizol pharmacokinetics and pharmacodynamics after single and repeated administrations in arthritic rats

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**Abstract** Combined administration of certain doses of opioid compounds with a non-steroidal anti-inflammatory drug can produce additive or supra-additive effects while reducing unwanted effects. We have recently reported that co-administration of metamizol with tramadol produces antinociceptive effect potentiation, after acute treatment. However, none information about the effect produced by the combination after chronic or repeated dose administration exists. The aims of this study were to investigate whether the antinociceptive synergism produced by the combination of metamizol and tramadol (177.8 + 17.8 mg/kg, s.c. respectively) is maintained after repeated treatment and whether the effects observed are primarily due to pharmacodynamic interactions or may be related to pharmacokinetics changes. Administration of metamizol plus tramadol acute treatment significantly enhanced the antinociceptive effect of the drugs given alone ($P < 0.05$). Nevertheless, this effect decreased about 53% after the chronic treatment (3 doses per day, for 4 days). No pharmacokinetic interaction between metamizol and tramadol was found under acute treatment ($P > 0.05$). The mechanism involved in the synergism of the antinociceptive effect observed with the combination of metamizol and tramadol in single dose cannot be attributed to a pharmacokinetic interaction, and other pharmacodynamic interactions have to be considered. On the other hand, when metamizol and tramadol were co-administered under repeated administrations, a pharmacokinetic interaction and tolerance development occurred. Differences found

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in metamizol active metabolites' pharmacokinetics ($P < 0.05$) were related to the development of tolerance produced by the combination after repeated doses. This work shows an additional preclinical support for the combination therapy. The clinical utility of this combination in a suitable dose range should be evaluated in future studies.



## 1. Introduction

Opioid drugs remain the common choice for the treatment of pain of moderate to severe intensity. However, the usefulness of these drugs in treating chronic pain is limited due to the development of tolerance to the analgesic effect that occurs after repeated administrations, resulting in escalation of the dose administered and therefore to an increased incidence of adverse effects (Gammaitoni et al., 2003; Domínguez-Ramírez et al., 2010). A common strategy to maintain adequate analgesic effects and to reduce the adverse effects is to combine doses of opioid compounds with nonsteroidal anti-inflammatory drugs (NSAIDs). In certain combinations of these drugs, it has been shown that it is not only possible to reduce the risk of incidence of adverse effects associated with the administration of high doses of the individual drugs, but also the antinociceptive effects are increased (Hernández-Delgadillo et al., 2003; López-Muñoz et al., 2004). Although some clinical and preclinical studies showing that combinations between opioids and NSAIDs can produce analgesic potentiation, little is known about the antinociceptive effects of repeated administrations. Some studies have shown good efficacy of the combination of tramadol and metamizol under preclinical conditions (Planas et al., 2003; Poveda et al., 2003). Metamizol and tramadol are analgesic drugs with complex mechanisms of action, extensively used in combination in the management of acute postoperative pain in humans (Poveda et al., 2003). The pharmacodynamic mechanism for the interaction between metamizol and tramadol could be attributed partially to their participation in the opioidergic system (Vasquez and Vanegas, 2000; López-Muñoz et al., 2013a). Other mechanisms such as the L-arginine-NO-cyclic GMP pathway and interaction with N-methyl D-aspartic acid receptors could be proposed to explain the antinociceptive synergism observed with the combination of such drugs. In a previous study, 25 different combinations of metamizol and tramadol were analyzed using the model of "pain-induced functional impairment in rat" (PIFIR) after a single dose administration, and the results as antinociceptive effects were additive or potentiative, for all the combinations studied (López-Muñoz et al., 2013a).

Tramadol is a central analgesic drug with a low affinity for opioid receptors. Tramadol is metabolized in the liver by two principal pathways: O-demethylation to O-desmethyltramadol (M1) by CYP2D6 and N-desmethylation to N-desmethyltramadol (M2) by CYP2B6 and CYP3A4. Only one of tramadol metabolites, M1, is pharmacologically active. Its selectivity for μ receptors has recently been demonstrated, showing a higher affinity for opioid receptors than the parent drug (Scott and Perry, 2000). Metamizol is a nonsteroidal anti-inflammatory drug that acts as an effective analgesic and antipyretic agent. Metamizol is a pyrazolone derivative that inhibits the synthesis of prostaglandins at central and peripheral levels (Alves and Duarte, 2002; Ortiz et al., 2003), and it is also known that its antinociceptive effects are mediated at least in part by central mechanisms (Hernández and Vanegas, 2001). Metamizol is a pro-drug that undergoes hydrolysis to yield 4-methylaminoantipyrine (MAA), which is transformed in the liver by cytochrome CYP3A4 to 4-aminoantipyrine (AA) and by oxidation to 4-formylaminoantipyrine (FAA). AA is acetylated to 4-acetylaminoantipyrine (AAA). MAA and AA produce a dose-dependent antinociceptive effect in arthritic rats (PIFIR model), whereas the other metabolites are inactive (López-Muñoz et al., 2013b).

It may be possible that metamizol and tramadol could compete for the same enzymes, causing changes in the concentrations of metabolites of metamizol and consequently in the pharmacological effects produced. The aims of this study were to investigate the antinociceptive synergism produced by the combination of metamizol and tramadol (17.8 + 177.8 mg/kg, s.c. respectively) in an acute and chronic administration schedules and if the effects produced are mainly due to pharmacodynamic interactions or may be related to pharmacokinetic changes in the two main active metabolites of metamizol.

## 2. Materials and methods

### 2.1. Animals

Male Wistar rats [Crl (WI)fBR] from the Production Unit of Laboratory Animal Species of the Metropolitan Autonomous University, weighing 180–220 g, were used. Animals were housed in an animal room with controlled temperature (22 ± 2 °C) under a light–dark cycle of 12 h. Rats were provided with standard chow (Purina Laboratory Rodent Diet 5001, Pet Food, México City, México) and water *ad libitum*. In the 12 h before the experiments, food was withheld, leaving only free access to water. Experiments were performed during the light phase and animals were used only once.

All experimental procedures were approved by the local Institutional Animal Care and Use Committee in accordance with the Mexican federal regulations for the care and use of laboratory animals NOM-062-ZOO-1999 (Mexican Ministry of Health), the Guidelines on Ethical Standards for Investigations of Experimental Pain in Animals (Zimmermann, 1983), the Committee for Research and Ethical Issues of the International Association for the Study of Pain (Covino et al., 1980) and adhere to the Guide for Care and Use of Laboratory Animals, Washington, D.C. (2011). The number of experimental animals was kept to a minimum. At the conclusion of the study, rats were euthanized with $CO_2$ to avoid unnecessary suffering.