ABSTRACT

This study was designed to evaluate the antinociceptive interaction of the tramadol–meloxicam combination in different proportions (tramadol + meloxicam in 1:1, 1:3, and 3:1 ratios), as well as the role of nitric oxide, opioidergic, and serotonergic pathways in the antinociceptive effect of the combination. The effects of individual drugs and fixed-ratio combinations were assayed using the 3% formalin test in mice. Isobolographic analysis was employed to characterize the synergism produced by the combinations. Tramadol (3.16–10 mg/kg, i.m.), meloxicam (3.16–17.8 mg/kg, i.m.), and tramadol–meloxicam combinations produced a dose-dependent antinociceptive effect. ED_{30} values were estimated for the individual drugs, and isobolograms were constructed. The tramadol + meloxicam 1:1 and 1:3 ratio combinations showed synergistic interactions while the 3:1 ratio produced additive effects. Naloxone (1 mg/kg, i.m.) or methiothepin (0.1 mg/kg, i.m.), but not L-NAME (3 mg/kg, i.m.), prevented the antinociceptive effects of the combination. These data suggest that (1) the tramadol–meloxicam combination produces a functional synergistic interaction that involves both opioid and serotonin receptors, and (2) this combination may be a promising tool in pain management. Drug Dev Res 73: 43–50, 2012. © 2011 Wiley Periodicals, Inc.

Key words: tramadol; meloxicam; synergism; opioid receptors; serotonin receptors

INTRODUCTION

Opioids remain the most effective therapy available for the treatment of moderate to severe pain in humans. However, the problems arising from unwanted side effects persist. Thus, combinations of opioids and other analgesic drugs are commonly used to control postoperative pain. The potential advantage of using combination therapy is that the analgesic effects can be maximized, whereas the incidence of side effects could be minimized. In addition, the multiplicity of mechanisms involved in pain suggests...