

Author's Accepted Manuscript

Administration of a co-crystal of tramadol and celecoxib in a 1:1 molecular ratio produces synergistic antinociceptive effects in a postoperative pain model in rats

Manuel Merlos, Enrique Portillo-Salido, Alex Brenchat, Bertrand Aubel, Jordi Buxens, Angels Fisas, Xavier Codony, Luz Romero, Daniel Zamanillo, José Miguel Vela



PII: S0014-2999(18)30353-4
DOI: <https://doi.org/10.1016/j.ejphar.2018.06.022>
Reference: EJP71852

To appear in: *European Journal of Pharmacology*

Received date: 23 September 2017
Revised date: 18 June 2018
Accepted date: 18 June 2018

Cite this article as: Manuel Merlos, Enrique Portillo-Salido, Alex Brenchat, Bertrand Aubel, Jordi Buxens, Angels Fisas, Xavier Codony, Luz Romero, Daniel Zamanillo and José Miguel Vela, Administration of a co-crystal of tramadol and celecoxib in a 1:1 molecular ratio produces synergistic antinociceptive effects in a postoperative pain model in rats, *European Journal of Pharmacology*, <https://doi.org/10.1016/j.ejphar.2018.06.022>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Administration of a co-crystal of tramadol and celecoxib in a 1:1 molecular ratio produces synergistic antinociceptive effects in a postoperative pain model in rats^{*}**Merlos, Manuel^{*}; Portillo-Salido, Enrique; Brenchat, Alex; Aubel, Bertrand; Buxens, Jordi; Fisas, Angels; Codony, Xavier; Romero, Luz; Zamanillo, Daniel; Vela, José Miguel**

Drug Discovery and Preclinical Development, Laboratorios del Dr. Esteve, S.A.U., Parc Científic de Barcelona, Baldiri Reixac 4-8, 08028 Barcelona, Spain.

^{*}Corresponding author. Manuel Merlos Postal address: Drug Discovery and Preclinical Development, Laboratorios del Dr. Esteve, S.A.U., Parc Científic de Barcelona, Baldiri Reixac 4-8, 08028 Barcelona, Spain. Tel.:+34 934466068. mmerlos@esteve.com

Abstract

Drug combination for the treatment of pain is common clinical practice. Co-crystal of Tramadol-Celecoxib (CTC) consists of two active pharmaceutical ingredients (APIs), namely the atypical opioid tramadol and the preferential cyclooxygenase-2 inhibitor celecoxib, at a 1:1 molecular ratio. In this study, a non-formulated 'raw' form of CTC administered in suspension (referred to as ctc_{susp}) was compared with both tramadol and celecoxib alone in a rat plantar incision postoperative pain model. For comparison, the strong opioids morphine and oxycodone, and a tramadol plus acetaminophen combination at a molecular ratio of 1:17 were also tested. Isobolographic analyses showed that ctc_{susp} exerted synergistic mechanical antiallodynic (experimental $ED_{50}=2.0\pm 0.5$ mg/kg, i.p.; theoretical $ED_{50}=3.8\pm 0.4$ mg/kg, i.p.) and thermal (experimental $ED_{50}=2.3\pm 0.5$ mg/kg, i.p.; theoretical $ED_{50}=9.8\pm 0.8$ mg/kg, i.p.) antihyperalgesic effects in the postoperative pain model. In contrast, the tramadol and acetaminophen combination showed antagonistic effects on both mechanical allodynia and thermal hyperalgesia. No synergies between tramadol and celecoxib on locomotor activity, motor coordination, ulceration potential and gastrointestinal transit were observed after the administration of ctc_{susp} . Overall, rat efficacy and safety data revealed that ctc_{susp} provided synergistic analgesic effects compared with each API alone, without enhancing adverse effects. Moreover, ctc_{susp} showed similar efficacy but improved safety ratio (80, measured as

^{*} Medical writing support for this manuscript was provided by Aspire Scientific Ltd, Bollington, UK and was funded by Mundipharma Research GmbH & Co.KG (Limburg, Germany).

Download English Version:

<https://daneshyari.com/en/article/8528955>

Download Persian Version:

<https://daneshyari.com/article/8528955>

[Daneshyari.com](https://daneshyari.com)