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Comparison between oral and intra-articular antinociceptive effect of dexketoprofen and tramadol combination in monosodium iodoacetate-induced osteoarthritis in rats

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ABSTRACT

Dexketoprofen and tramadol, alone or in combination, were evaluated after oral or intra-articular administration on knee osteoarthritis nociception induced by intra-articular (i.ar.) monosodium iodoacetate (MIA, 1 mg/25 μl) in the rat right knee while the left knee received saline (25 μl). Seven days after MIA treatment, dexketoprofen, tramadol, their combination or the vehicle were administered. Nociception was evaluated as alteration in hind limb weight distribution with Incapacitance tester at different time-points after drug administration. Oral dexketoprofen (0.1–1 mg/kg) or tramadol (0.5–5 mg/kg) induced maximal antinociception at 1 and 5 mg/kg, respectively. Their combination dose-dependently increased the intensity and duration of antinociception, that was additive and lasted up to 3 days. Also the intra-articular administration of dexketoprofen or tramadol (10–100 μg/25 μl) inhibited MIA-induced nociception, and the combination of the lower doses (10 μg/25 μl) produced a long lasting more than additive antinociceptive effect indicating a synergistic interaction between the two drugs. This effect was significantly reduced by naloxone (10 μg/25 μl, i.ar.) co-administered with both compounds. The intra-articular administration of both drugs at 10 μg/25 μl in the contralateral control knee joint provoked a marked synergistic antinociceptive effect indicating significant systemic diffusion through synovial membrane. The oral or intra-articular combination of dexketoprofen and tramadol produced additive or synergistic antinociceptive effects, respectively, in the model of MIA-induced osteoarthritis in rats, that might allow to obtain therapeutic advantages with lower side effects.

1. Introduction

Osteoarthritis is a degenerative disease characterized by structural changes of the knee joint including articular cartilage erosion, synovitis and remodeling of subchondral bone. Patients affected by osteoarthritis experience pain that worsens with motion and exercise and, with pathology progression, also at rest (Hunter and Felson, 2006). Pharmacological treatments of osteoarthritis aim to reduce pain in order to increase the patient's joint function and quality of life. Non steroidal anti-inflammatory drugs (NSAIDs) and opioids are widely used in this pathology but side effects like gastrointestinal tract damage for the first, and central side effects including sedation, respiratory depression and nausea, for the latter, hamper their chronic administration (Hinton et al., 2002; Manchikanti et al., 2010). Combinations of opioids and NSAIDs at low doses, for which side effects are lower, have been shown to induce synergistic increase of antinociception in different animal models of pain (Fletcher et al., 1997; Lashbrook et al., 1999; García-Hernández et al., 2007; Miranda et al., 2008).

Experimental osteoarthritis induced by MIA is characterized by a marked and long lasting nociceptive response that is stable for a long period (Cialdai et al., 2009). MIA is a metabolic inhibitor of glycolysis in chondrocytes that causes loss of articular cartilage, synovial inflammation and changes of subchondral bone that closely resemble the lesions of the human pathology (Guingamp et al., 1997; Guzman et al., 2003; Pomonis et al., 2005; Ivanavicius et al., 2007).

The drugs investigated in this study have two different mechanisms of action. Tramadol is an atypical opioid which acts by the central activation of μ-opioid receptors and by inhibiting the neuronal uptake of norepinephrine and serotonin (Raffa et al., 1991). Dexketoprofen is the active S(+)-enantiomer of the racemic ketoprofen, a NSAID with non-selective cyclooxygenase (COX) inhibitory activity whose antinociceptive effects are attributed to the inhibition of the synthesis of prostaglandins, associated with a reduced incidence of gastrointestinal bleeding (Ferreira and

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Nakamura, 1979; Smith et al., 2000; Barbanoj et al., 2001; Moore and Barden, 2008).

The administration of opioids or NSAIDs alone has been shown to be effective against osteoarthritis pain in humans (Beltran et al., 1998; Thorne et al., 2008) and in MIA-induced osteoarthritis in rats (Bove et al., 2003; Combe et al., 2004; Chandran et al., 2009). In particular, NSAIDs are mainly effective in nociception induced by MIA at rest (Bove et al., 2003) while tramadol is mainly effective after exercise (Chandran et al., 2009) and mildly at rest (Combe et al., 2004). The efficacy of dexketoprofen and tramadol in the different nociceptive conditions has prompted us to test the combination of the two drugs in MIA-induced osteoarthritis nociception in rats since the effect of their combination has not yet been tested in this experimental model.

This study aimed to evaluate the antinociceptive effect of dexketoprofen and tramadol in combination after oral and intra-articular administration on MIA-induced knee joint osteoarthritis in rats and to investigate the type of drug interaction at low effective doses.

2. Materials and methods

2.1. Induction of experimental osteoarthritis

This study was performed according to the principles and guidelines of the European Union, Italian government regulations, and the local ethics committee.

Male Wistar rats (Harlan Laboratories, Udine, Italy) weighing 200–250 g were anaesthetized with pentobarbital (40 mg/kg, i.p.) and received a single injection of MIA (1 mg/25 μl) in the joint space of the right knee through the infrapatellar ligament. The left knee received an equal volume of 0.9% saline (vehicle).

MIA solution was prepared in sterile conditions through filtration with a 0.22 μm filter (Millex-GV, Millipore, Ireland) and administered using a 50 μl Hamilton syringe with a 27 G needle.

2.2. Evaluation of nociception

Nociception associated with osteoarthritis was characterized by changes in weight distribution on hind paws. A hind limb weight bearing apparatus (Incapacitance tester, Linton Instrumentation, Norfolk, UK) was used to assess the difference in the distribution of body weight between the right (osteoarthritis) and the left (contralateral control) hind limb. Animals were placed in the plexiglass chamber with each hind paw on the separate force plate and allowed to get used to the apparatus. When stationary, the force exerted by each hind paw on the respective plate was registered over a period of 5 s and expressed in grams. A total of four recordings were taken for each rat.

2.3. Oral dexketoprofen, tramadol and their combined administration

Dexketoprofen (0.1–0.25–0.5–1 mg/kg), tramadol (0.5–1.25–2.5–5 mg/kg), their combination (0.1+0.5; 0.25+1.25; 0.5+2.5; 1+5 mg/kg dexketoprofen+tramadol, respectively) or water (vehicle) were orally administered on day 7 after MIA treatment when nociception reached a plateau. Nociception was measured with Incapacitance tester at 1–3–6 h and 1–3–6 days after drugs administration.

2.4. Intra-articular dexketoprofen, tramadol and their combined administration

Dexketoprofen (10–30–100 μg/25 μl), tramadol (10–30–100 μg/25 μl), their combination (10+10 μg/25 μl) or 0.9% saline (vehicle) were administered intra-articularly on day 7 after MIA (1 mg/25 μl) injection in the right knee, while the left knee received 0.9% saline. Nociception was measured with Incapacitance tester at 1–3–7–10–14–17–21 days after drugs administration.

In order to evaluate a possible systemic diffusion of drugs after local treatment, dexketoprofen (10 μg/25 μl), tramadol (10 μg/25 μl), their combination (10+10 μg/25 μl) or 0.9% saline (vehicle) were administered on day 7 in the contralateral, left knee (control) of MIA treated rats, while the right knee received 0.9% saline. Nociception was measured at 1–3–7–10–14 days after drug administration.

2.5. Intra-articular naloxone on dexketoprofen and tramadol antinociceptive effect

This series of experiments was performed to check the involvement of opioid receptors in the synergistic antinociception produced by dexketoprofen and tramadol. The intra-articular administration of the compounds alone (10 μg each/25 μl), or in combination with naloxone (10 μg/25 μl) was performed 7 days after MIA (1 mg/25 μl i.ar.) treatment. The effect of drugs on nociception was evaluated with Incapacitance tester 1 day after administration and was compared to the effect of dexketoprofen, tramadol and their combination.

2.6. Data analysis

Data were first analyzed as the difference in weight distribution (g) between the left and the right hind limbs (left-right) and then drugs′ effect calculated as percent of inhibition of the respective basal value.

Statistical comparison among groups was performed with a two way ANOVA followed by Bonferroni test for multiple comparisons or by Student′s *t*-test, where appropriate. The differences were considered significant at the level of $P < 0.05$.

2.7. Drugs and chemicals

Dexketoprofen trometamol was obtained from Lusochimica S.p.A (Pisa, Italy) and tramadol hydrochloride from Arevipharma GmbH (Dresden, Germany). Naloxone, monosodium iodoacetate and sodium pentobarbital were purchased from Sigma-Aldrich (St. Louis, MO).

3. Results

3.1. Effect of oral administration of dexketoprofen or tramadol on MIA-induced nociception

The oral administration of dexketoprofen or tramadol produced a dose-dependent reduction of the nociceptive response induced by MIA that was statistically different from control group only at the higher doses tested (1 mg/kg and 5 mg/kg, respectively) while the antinociceptive effect induced by the lower doses (0.1–0.5 mg/kg for dexketoprofen and 0.5–2.5 mg/kg for tramadol) did not significantly affect the nociceptive response in MIA-treated groups (Fig. 1).

Dexketoprofen showed a maximum and statistically significant antinociceptive effect by 41 ± 8% ($n=6$), 6 h after the administration of 1 mg/kg (Fig. 1A). Tramadol, at the higher dose of 5 mg/kg,