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Pharmacodynamic differences between racemic ibuprofen and dexibuprofen in murine preclinical study

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the best therapeutic options to treat pain, but their use is restricted by their adverse effects. In this study, the pharmacological profile of ibuprofen and dexibuprofen was evaluated using the murine acetic acid writhing test, and the participation of naltrexone, naltrindole, nor-binaltorphimine, L-NAME, risperidone, and tropisetron in the antinociceptive efficacy. Antinociception was assessed by dose–response curves to ibuprofen and dexibuprofen before and after the i.p. administration of 1,0 mg/kg of naltrexone, or naltrindole, or norbinaltorphimine, or 5 mg/kg of L-NAME, 0,5 mg/kg of risperidone, or tropisetron in the murine assay. Results are presented as means ± SEM and differences calculated by one-way ANOVA followed by Tukey's post-test. Ibuprofen and dexibuprofen produced a dose-dependent antinociceptive effect with different potency. After pretreatment of mice with naltrexone, naltrindole, nor-binaltorphimine, L-NAME, risperidone, or tropisetron, a significant increase in ibuprofen efficacy was obtained, however, no effect on dexibuprofen activity was obtained. Data demonstrate that ibuprofen and dexibuprofen induce effective antinociception in the acetic acid writhing test, either directly, through COX inhibition, or indirectly, through the modulatory effects of opioid or serotonin, or nitric oxide receptors. These actions are complex since the effects depending on the chemical structure of the NSAID. Thus, a racemic compound (ibuprofen) induces a significant increase in nociceptive efficacy. However, they have no effect on the dextrorotatory enantiomer (dexibuprofen).

Keywords: Ibuprofen; Dexibuprofen; Writhing test; Antinociception

1 Introduction

For a long time, the treatment of pain has been based mainly on the use of opioids and non-steroidal anti-inflammatory drugs (NSAIDs). According to their chemical structure and pharmacological properties, NSAIDs can be classified into different categories, among which are the propionic acid derivatives, to which naproxen, ketoprofen, flurbiprofen, ibuprofen, and dexibuprofen belong.

NSAIDs act mainly by inhibiting the activity of cyclooxygenases (COXs) and then decrease the production of prostanoids: prostacyclins, thromboxanes, and prostaglandins. The existence of three isoforms of COXs has been reported: COX-1, COX-2, and COX-3, which participate in the analgesic, anti-inflammatory, and antipyretic effects of NSAIDs as well as in

the adverse effects of NSAIDs and also in other physiological processes, such as the regulation of vascular tone, platelet function, gastric mucosa, renal and hepatic system [1-3]

Specific NSAIDs have been developed to inhibit COXs, including acetic acid derivatives, such as ibuprofen, which is a racemic drug that inhibits both the COX-1 and COX-2 isoforms, formed by the dextrorotatory enantiomer with S (+) configuration with high antinociceptive power activity called dexibuprofen and another R (-) enantiomer with slight analgesic activity [4].

The pharmacologically active dextrorotatory enantiomer of racemic ibuprofen possesses strong pharmacological activity than racemic ibuprofen as it reduces gastric damage and enhances analgesic and anti-inflammatory activity [5]. Likewise, its reliable use in humans has been reported [6-7]. However, to date, limited data on the molecular mechanisms of action of dexibuprofen are available in the literature.

Various types of animal pain assays are available to characterize the pharmacological profile of analgesic agents, including formalin administration, hot plate, tail flick, writhing, and other tests. One of the most used is the acetic acid writhing test, which is a tonic visceral pain that mimics a type of human pain and uses a chemical stimulus, a dilution of acetic acid, to induce a characteristic behavior of pain. In this test, the chemical stimulus induces a wave of contraction of the abdominal muscle followed by extension of the hindlimbs (writhes) and reduction in motor activity [8-9].

In this study, the antinociceptive activity of ibuprofen and dexibuprofen was examined in the acetic acid writhing test in mice, and the role of naltrexone, naltrindole, nor-binaltorphimine, L-NAME, risperidone, and tropisetron in this antinociception was evaluated.

2 Material and methods

2.1 Animals

Male CF-1 mice (25–30 g) from the Central Animal Facility of the Universidad de Chile Faculty of Medicine were used. Animals were kept under a 12-h light–dark cycle at 22 ° ± 1° C with free access to food and water. All animal procedures were performed in accordance with the ethical guidelines of the International Association for the Study of Pain and approved by the Animal Care and Use Committee of the Faculty of Medicine (CBA 0852/FMUCH/2018). Research involving animals complied with all relevant national regulations and institutional policies for the care and use of animals. Mice were acclimatized to the laboratory for at least 1 h before testing, used only once during the protocol, and euthanized after the algesimeter test with an intraperitoneal (i.p.) injection of 60 mg/kg of pentobarbital. The minimum number of animals required to establish consistent effects of drug treatment and minimize animal suffering was used.

2.2 Measurement of antinociceptive activity

Antinociception was assessed by the acetic acid writhing test (WT) as described previously [8]. Mice were injected i.p. with 10 ml/kg of 0.6% acetic acid solution, and the number of writhes were counted for the next 5 min. The drugs were administered 30 min prior to the acetic acid injection. Antinociception was expressed as percentage of maximun possible effect (% MPE) of the number of writhes observed in control mice injected (22.10 ± 1.8, n = 12).

2.3 Experimental design

The antinociceptive activity of ibuprofen and dexibuprofen was evaluated from dose response curves of drugs were administered i.p. 30 min prior to test. Dose–response curves were obtained before and after the i.p. administration of 1,0 mg/kg of naltrexone (NTX), or naltrindole (NTI) or norbinaltorphimine (nor-BNI), or 5 mg/kg of L-NAME, 0,5 mg/kg of risperidone (RISPER) or tropisetron (TROPI) in the WT assay, using at least 6-8 animals for each of at least 4 doses. The doses used were selected according to previously published studies [8, 9] and adjusted according to preliminary experiments.

2.4 Drugs

Drugs were freshly dissolved in sterile physiological saline solution of 10 ml/kg, for i.p. administration. Ibuprofen and dexibuprofen were y provided by local laboratories and naltrexone, naltrindole, norbinaltorphimine. L-NAME, risperidone and tropisetron from Sigma-Aldrich Chemical Co, USA.

2.5 Statistical analyses

Results are presented as means ± standard error of the mean (SEM). The statistical differences between the results were assessed by one-way analyses of variance (ANOVA) followed by Tukey's post-test; P values less than 0.05 ($P < 0.05$) were considered to reflect statistically significant differences. Statistical analyses were carried out using the program Pharm Tools Pro, version 1.27, McCary Group Inc., PA, USA.

3 Results

3.1 Antinociception induced ibuprofen and dexibuprofen

The i.p. administration of ibuprofen or dexibuprofen produced a dose- related antinociceptive effects with different potencies in the WT test. Treatment with dexibuprofen was 1.1 times more potent that ibuprofen. These results are shown in Table 1 and depicted graphically in Figure 1**.**

Table 1 Number of writhes (mean ± SEM) of ED_{50} and analgesic ratio (AR) for the antinociceptive activity of ibuprofen and dexibuprofen in mice acetic acid writhing test before and after pretreatment with 1 mg/kg of naltrexone (NTX), or naltrindole (NTI) or nor-binaltorphimine (nor-BNI), 5 mg/kg i.p. of L-NAME, 0.5 mg/kg of risperidone (RISPER) or 0.5 mg/kg of tropisetron (TROPI).

Table 1 Number of writhes (mean ± SEM) of ED_{50} and analgesic ratio (AR) for the antinociceptive activity of ibuprofen and dexibuprofen in mice acetic acid writhing test before and after pretreatment with 1 mg/kg of naltrexone (NTX), or naltrindole (NTI) or nor-binaltorphimine (nor-BNI), 5 mg/kg i.p. of L-NAME, 0.5 mg/kg of risperidone (RISPER) or 0.5 mg/kg of tropisetron (TROPI).

Condition	Ibuprofen	Dexibuprofen	ar
Control	8.7 ± 0.7	10.2 ± 1.7	1.1
Plus NTX	1.8 ± 0.1*	9.1 ± 1.1	5.0
Plus NTI	4.5 ± 1.0*	9.6 ± 0.6	2.1
Plus nor-BNI	5.0 ± 1.1*	9.2 ± 0.3	1.8
Plus L-NAME	2.2 ± 0.4*	11.3 ± 1.6	5.1
Plus RISPER	2.7 ± 0.8*	12.8 ± 1.7	4.7
Plus TROPI	2.5 ± 0.7*	11.8 ± 0.9	4.7

AR: relation between dexibuprofen/ibuprofen. ✱: P>0.05 compared with control.

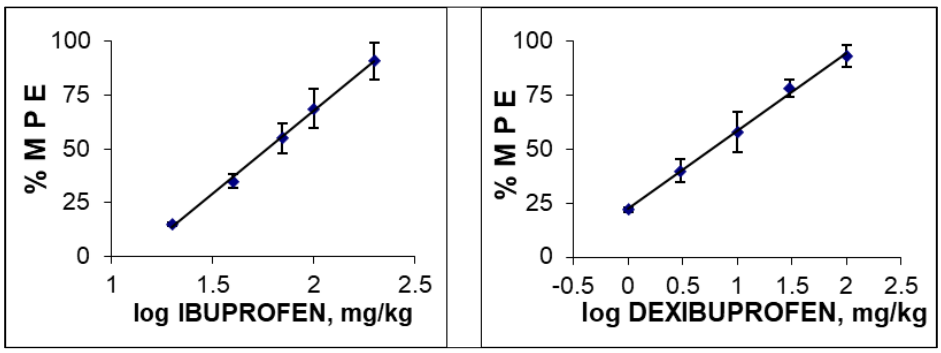

Figure 1 Dose response curves for the antinociceptive activity of ibuprofen and dexibuprofen in the acetic acid writhing test of mice. Each point is the mean ± SEM of 6-8 mice. % MPE: antinociception as percentage of the maximun possible effect

3.2 Effect of opioid antagonists on the antinociception of ibuprofen and dexibuprofen

Mice treated with 1 mg/kg. i.p. of NTX, or NTI or nor-BNI. did not exhibit significant differences in behavior or locomotor activity compared to controls. To determine the effect of opioid antagonists in the potency of ibuprofen and

dexibuprofen in the WT, complete dose response curves were obtained for in mice pretreated with NTX, or NTI or nor-BNI. The data revealed a significant increase in the analgesic effect of ibuprofen; however, no differences were detected with dexibuprofen (see Table 1 and Figure 2 and 3). In addition, the changes in the ED_{50}, expressed as the ratio between the ED_{50} values, varied between 1.8 and 5.0, as shown in Table 1.

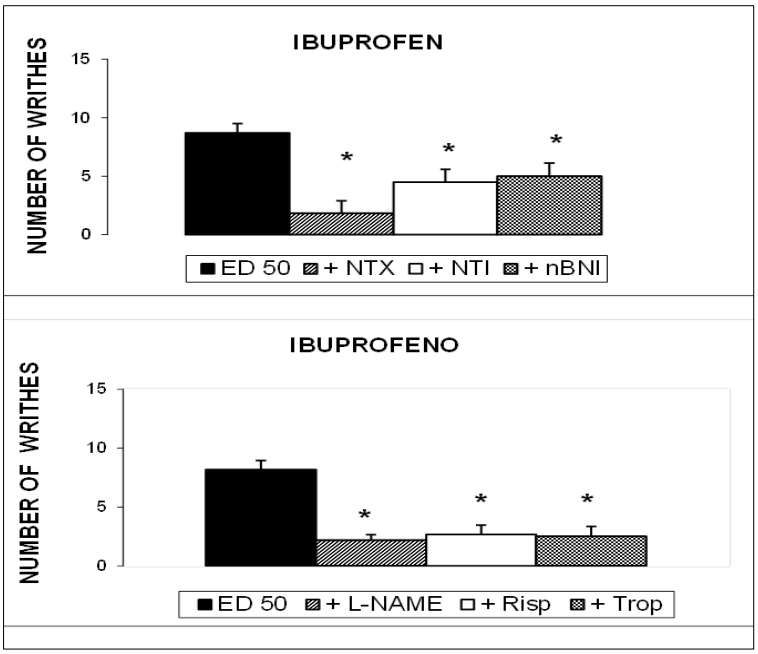

Figure 2 Representative histograms of number of writhes induced by ED_{50} of ibuprofen in the acetic acid writhing test of mice after the pretreatment with naltrexone (NTX), naltrindole (NTI), nor-binaltorphimine (nBNI), L-NAME, risperidone (Risp) and tropisetron (Trop). (n = 6-8, mean ± SEM). * p< 0.005 compared with the control ED50

3.3 Effect of or L-NAME, risperidone and tropisetron on the antinociception of ibuprofen and dexibuprofen

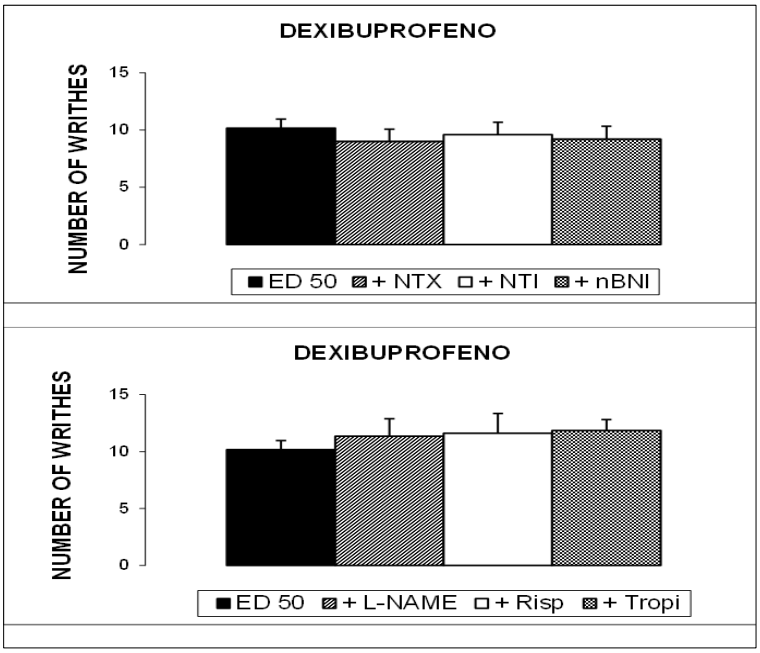

Figure 3 Representative histograms of number of writhes induced by ED_{50} of dexibuprofen in the acetic acid writhing test of mice after the pretreatment with naltrexone (NTX), naltrindole (NTI), nor-binaltorphimine (nBNI), L-NAME, risperidone (Risp) and tropisetron (Trop). (n = 6-8, mean ± SEM)

Mice treated with 5 mg/kg of L-NAME, or 0.5 mg/kg of RISPER or TROPI did not exhibit significant differences in behavior or locomotor activity compared to controls. To determine the effect of L-NAME or RISPER or TROPI in the potency of ibuprofen and dexibuprofen in the WT, complete dose response curves were obtained for in mice pretreated with L-NAME or RISPER or TROPI.

3.4 Effect of or L-NAME, risperidone and tropisetron on the antinociception of ibuprofen and dexibuprofen

Mice treated with 5 mg/kg of L-NAME, or 0.5 mg/kg of RISPER or TROPI did not exhibit significant differences in behavior or locomotor activity compared to controls. To determine the effect of L-NAME or RISPER or TROPI in the potency of ibuprofen and dexibuprofen in the WT, complete dose response curves were obtained for in mice pretreated with L-NAME or RISPER or TROPI. The data revealed a significant increase in the analgesic effect of ibuprofen; however, no differences were detected with dexibuprofen (see Table 1 and Figure 2 and 3). In addition, the changes in the ED_{50}, expressed as the ratio between the ED_{50} values, varied between 4.7 and 5.1, as shown in Table 1.

4 Discussion

NSAIDs are frequently used as pharmacotherapy in the treatment of pain, but their ceiling effect and their adverse effects restrict their use. For these reasons, the enantiomers of racemic NSAIDs have been used in the treatment of analgesia. The objective of the present study, using a murine visceral model of pain, was determine whether naltrexone, naltrindole, nor-binaltorphimine, L-NAME, risperidone and tropisetron are involved in the antinociception induced by dexibuprofen.

The results presented herein confirm the analgesic efficacy, reported in the literature, for both ibuprofen and dexibuprofen, in different animal pain assays, independently of the model or the nociceptive stimulus, either of tonic pain, as tail flick or hot-plate tests, or of phasic pain, as in the WT or formalin assays [5,8,12-17].

The outcomes obtained in this work seem to be related to the molecular structure of the analgesic agents used since one of them (ibuprofen) is a racemic compound and another (dexibuprofen) is only the dextrorotatory enantiomer of the racemic compound. The differences in the pharmacological effects obtained suggest a direct relationship with the chemical structural modifications previously indicated. Furthermore, the test used in this work has been used to describe the antinociceptive activity of various compounds and the involvement of a wide variety of mediators, including cannabinoids, opioid peptides, nitric oxide, interleukins, eicosanoids, neuropeptides, dopamine, epinephrine, serotonin, and others. [1-3]. The differences obtained with pretreatment with the opioid antagonists NTX, NTI, and nor-BNI could be explained by the molecular differences indicated above. A significant increase in the efficacy of ibuprofen with the aforementioned antagonists is described, however, they lack an effect on the antinociception induced by dexibuprofen. According to these results, it is suggested that the opioid receptors are involved in the activity of the racemic molecule only. Findings in agreement with previously published results for other NSAIDs [17- 21].

Among the pronociceptive mediators is nitric oxide (NO), involved in modulate complex mechanisms in nociception and inflammation, since is an important mediator of nociception and experimental and clinical evidences have demonstrated that NO is also capable of inducing analgesia. NO is generated by the activity of nitric oxide synthase that exists in three isoenzymes called NOS. L-NAME, a selective NOS inhibitor, induces a modulatory effect on the antinociceptive effects of NSAIDs, with actions increasing and others reducing nociceptive activity, depending on the pain model used and the NSAID group [21-23]. The results of this study are consistent with previous reports, as L-NAME induced a significant increase in the nociceptive efficacy of ibuprofen. Otherwise, a lack of effect on the activity of dexibuprofen was obtained. The discrepancy could be explained based on the difference in the chemical structures of the NSAIDs involved and by the contradictory role that NO displays in nociception.

The participation of the serotonergic system in the nociceptive modulation is complex since it depends on various factors, such as the distribution of receptors, the doses of agonists or antagonists, the route of administration, and the type and duration of pain. It depends on these factors that the 5-HT1, 5-HT2, 5-HT3, and 5-HT7 receptors induce inhibitory, increase, or maintenance of the nociceptive response [24]. The results of this work are concordant with previous reports, since they show that the pretreatment of mice with tropisetron, a selective antagonist of 5HT3 increased the antinociception induced by ibuprofen, however, did not modify the efficacy of dexibuprofen. Similar results were obtained with pretreatment with risperidone, a 5HT2 antagonist.

The antinociceptive effects and the modulatory activity obtained by ibuprofen and dexibuprofen in the acetic acid writhing test could be explained, not only due to the primary inhibitory mechanisms of COX-1 and COX-2. The effects seem to be mediated by the participation of some of the other mechanisms of action that have been described associated

with ibuprofen and dexibuprofen, such as the participation of plasma levels of β-endorphin [4], NO [18], serotonergic receptors [24], the TRPA1 channel [19], amyloid beta peptide (Aβ142) [25], Rho A signalling [26], tumor necrosis α (TNFα), amyloid precursor protein (APP), β-secretase 1 (BACE1), and facilitating amyloid beta (Aβ) [27].

The results presented are not only interesting for the antinociceptive aspect, since NSAIDs, in addition to controlling pain and inflammation, are involved in cancer prevention and chemoprevention. Among them, dexibuprofen has special neurological activity and numerous reports show that the long-term use of NSAIDs induce a reduction in the risk of developing Alzheimer's disease, so its use in said disease has been proposed [28-30].

5 Conclusion

The data demonstrate that ibuprofen and dexibuprofen induce effective antinociception in acetic acid writhing test either directly, by COXs inhibition, or indirectly by modulatory effects of opioid or serotonin receptors or nitric oxide. These actions are complex and have different activities depending on the chemical structure of the agent in which they are used. Thus, they produce a significant increase in nociceptive efficacy in the racemic compound (ibuprofen), however, they have no effect with the dextrorotatory enantiomer (dexibuprofen).

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted without potential conflict of interest.

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Author contributions

All authors contributed directly and substantially to the study and approved the final version of the manuscript.

Statement of ethical approval

All animal procedures were performed in accordance with the ethical guidelines of the International Association for the study of pain and approved by the animal care and use committee of the Faculty of Medicine, University of Chile, (CBA 0852/FMUCH/2018).

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