



The synergistic antinociceptive effect of lornoxicam in combination with tramadol

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ABSTRACT

Introduction: One of the most important priorities in therapy is pain control. Therefore, many different groups of drugs are being used for this purpose, primarily opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Opioid analgesic tramadol, by binding to specific receptors, modulates the perception and response to painful stimuli and inhibits transmitting and further processing of pain impulses. Lornoxicam, which belongs to the oxcam class of NSAIDs, is a non-selective cyclooxygenase inhibitor with strong analgesic and anti-inflammatory effects, and better tolerance profile. Preliminary research, which requires further verification, suggests that lornoxicam may be a better alternative or adjunctive therapy to opioid analgesics in the treatment of moderate to severe pain. The aim of this study was to investigate antinociceptive effects of lornoxicam, as well as the combination of lornoxicam with tramadol.

Methods: Analgesic effect of combination of lornoxicam and tramadol or lornoxicam applied alone was examined on female albino mice, using a hot plate method. Measurements were made 30, 60, 90 and 120 minutes after intraperitoneal and subcutaneous administration, in dose of 10 mg/kg.

Results: Combination of lornoxicam and tramadol, applied intraperitoneally, increases the threshold of sensitivity to painful stimuli, which was not the case with subcutaneous administration.

Conclusions: Lornoxicam significantly increases analgesic effect when applied intraperitoneally in combination with tramadol. On the other hand, lornoxicam in combination with tramadol, did not increase the threshold of sensitivity to painful stimuli with significant difference, after subcutaneous administration.

Keywords: antinociceptive effect, tramadol, lornoxicam, combination of analgesics.

INTRODUCTION

Pain is defined by the *International Association for the Study of Pain* as „unpleasant sensory and emotional experience associated with actual or potential tissue

damage“, and it is caused by nociceptive stimulus. Although pain is a reaction of the body to harmful stimuli and is therefore a protective early warning system, the sensation of pain in postoperative patients has little positive effect. Hence, the term *pain*, derived from the Latin *poena* for punishment, reflects the deleterious effects that can be inflicted upon the body (1). The goal of postoperative pain relief is to achieve optimal analgesia, facilitating a quick return to normal physiological organ function

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with minimal side effects (2). Many different groups of drugs are being used in pain control, primarily opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).

Tramadol, a centrally acting analgesic, consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. Tramadol is effective as analgesics and seems to have a better profile of adverse effects than most opioids. Its analgesic efficacy can further be improved by combination with a non-opioid analgesic (3-5).

Lornoxicam is a new NSAID belonging to the oxicam class. Compared to the other NSAIDs, lornoxicam demonstrates strong analgesic and anti-inflammatory effects, along with an improved gastrointestinal toxicity profile. Its analgesic activity is comparable to that of opioids. High therapeutic potency is indicated in low doses, with a reduced risk of side effects (6-8). Preliminary research, which requires further confirmation, suggest that lornoxicam may be a better alternative or adjunctive therapy to opioid analgesics in the treatment of moderate to severe pain (9, 10).

Studies have also shown that opioids may act in synergy with some NSAIDs, and that such combinations may have therapeutic benefit in the clinical treatment of inflammatory pain (11). This effect is expected when combining analgesics that act at different areas along the route of painful stimulus, for example by combining nonsteroidal anti-inflammatory drug (NSAID), which operates mainly in the periphery, and opioid, which operates centrally. The objective of development of analgesics combination is to achieve efficacy, that is, to improve therapeutic effect while using lower dosages and having less side effects. (11, 12).

The use of combination of oral analgesics as opposed to an individual therapy offers potential benefits for the patients. Combining analgesics into a single product may facilitate prescribing and compliance by reducing the number of medicines that a patient must take during the pain control therapy. Combining products with different mechanism of action may provide multimodal approach in pain therapy, and, in addition, enable the individual agents potentially to act synergistically. Furthermore, with regard to safety, lower doses of each individual analgesic,

used in combination, may result in a lower incidence of individual adverse events (13).

The data obtained in one study indicated that the combination of atypical opioid tramadol and atypical NSAID propacetamol had more potent antinociceptive effects than those of tramadol and propacetamol, in mouse and rat models with acute and persistent pain. Study suggests that it is possible to increase the antinociceptive effects and decrease the undesirable side effects of tramadol, by coadministering propacetamol (14).

The fundamental concept that underlies the appropriate and successful management of pain by the use of opioid and nonopioid analgesics is individualization of analgesic therapy (15). During the development of multimodal analgesia, apart from increasing antinociception which was the primary goal, clinical evaluation of combinations' benefits should be based on the benefits coming from reduction of adverse effects of opioids in comparison to the side effects of non-opioids involved in such combination.

The aim of this study was to examine whether the coadministration of tramadol and lornoxicam change the threshold of sensitivity to painful stimuli and to examine the relationship between analgesia and method of application of the tested substances.

METHODS

Analgesic effects of lornoxicam in combination with tramadol was analysed on female albino mice, weighing 25-30 g. Four groups were formed, each consisting of ten mice. The sense of pain was induced by thermal stimulus by the method of hot plate. The temperature of the plate was constantly 55°C during the experiment. Analgesic effect was measured after a single intraperitoneal (i.p.) and subcutaneous (s.c.) administration of lornoxicam (in a dose of 10 mg/kg body weight), tramadol (in a dose of 10 mg/kg body weight) and their combination (lornoxicam and tramadol each in a dose of 10 mg/kg body weight) in time intervals of 30, 60, 90 and 120 minutes. Physiological solution in the same volume was administered to a control group.

The study was conducted on animal models (*in vivo*), in accordance with OECD, EPA regulation and *European convention for the protection of vertebrate animals used for experimental and other scientific purposes*.

Statistical analysis

Statistical analysis was done using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and

SPSS for Windows (version 20.0, SPSS Inc, Chicago, Illinois, USA). The Student's t-test was used in order to determine if two sets of data are significantly different from each other by calculating statistically significant difference between the two arithmetic means.

The results are presented in the diagram, showing the calculated mean (average of ten measurements), standard deviation and standard error (the ratio of the standard deviation and the square root of the number of measurements).

Calculated p value is based on a two-tailed distribution, comparing two sets of measurements of unequal variances. Level of significance was set at $p < 0.05$.

RESULTS

Latency period of lornoxicam was increased as compared to the control group after intraperitoneal administration (i.p.) and after subcutaneous administration (s.c.) as well. Lornoxicam applied intraperitoneally in dose of 10 mg/kg showed an analgesic effect, statistically different compared to the control group 60, 90 and 120 minutes after application ($p < 0.05$). However, 30 minutes after the i.p. application, the latency period of lornoxicam was increased, as compared to the control group, but with no statistically significant difference ($p = 0.053$). Subcutaneously applied lornoxicam showed analgesic effect compared to control group, in all observed time intervals ($p < 0.05$).

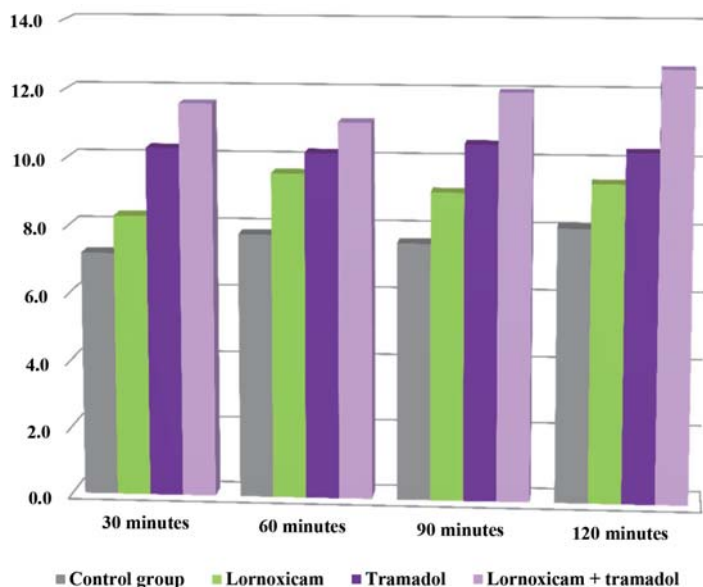


FIGURE 1. Comparison of analgesic effect of tested substances, after intraperitoneal administration

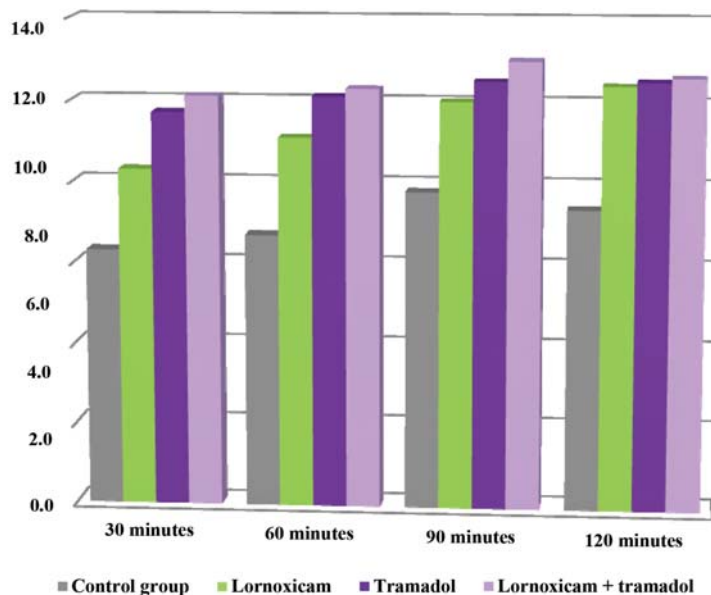


FIGURE 2. Comparison of analgesic effect of tested substances, after subcutaneous administration

The results have shown that lornoxicam in combination with tramadol, applied intraperitoneally, increase the threshold of sensitivity to painful stimuli, which was not the case with subcutaneous administration. Latency period of lornoxicam itself was 8.3, 9.6, 9.1 and 9.4 seconds, after 30, 60, 90 and 120 minutes respectively, after i.p. administration. On the other hand, latency period of lornoxicam in combination with tramadol was 11.6, 11.1, 12.0 and 12.7 seconds at the same measuring points. The calculated statistical difference for this combination was significant ($p < 0.05$).

Subcutaneously administrated lornoxicam showed the latency period of 8.3, 9.1, 10.0 and 10.4 seconds after 30, 60, 90 and 120 minutes respectively. Latency period of lornoxicam in combination with tramadol, administrated subcutaneously, was 10.1, 10.3, 11.0 and 10.6 seconds at the same measuring points. The calculated statistical difference for this method of application was significant only 30 minutes after application of tested combination ($p < 0.05$). At later time points (60, 90 and 120 minutes), calculated differences were $p = 0.063$, $p = 0.069$ and $p = 0.739$, respectively.

DISCUSSION

Studies have shown that the use of the combinations of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase their antinociceptive activity and improve the therapeutic effect, and lead to the use of lower doses of opioids, resulting in a reduction of side effects. Data obtained in the study carried out by Zhang et al (14) indicated that the combination of atypical opioid, tramadol and atypical NSAIDs, propacetamol had more potent antinociceptive effects than those of tramadol and propacetamol, in mouse and rat models, in the treatment of acute persistent pain. If propacetamol is used together with tramadol clinically, the dose of tramadol could be minimized and then enhance the analgesic effect. The study suggests that it is possible to increase the antinociceptive effects and decrease the undesirable adverse effects of tramadol by coadministering propacetamol.

Fernández - Dueñas et al. (16) investigated a synergistic interaction between fentanyl, tramadol and paracetamol, or whether the analgesic effect of this

mixture has increased activity compared to the very strong opioid fentanyl, and whether it leads to a reduction in the dose of fentanyl, and consequently reduced side effects. The results showed that there is a synergistic interaction between these three drugs in reducing nociception induced by acetic acid in mice. Such a multimodal approach also permits reducing the dose of fentanyl, and reduced the incidence of adverse effects, primarily gastrointestinal inhibition passage, which is a common side effect of opioid therapy.

Combinations of two analgesic drugs of the same or different class are widely used in clinical therapy to enhance its antinociceptive effects and reduce the side effects. Moreno-Rocha et al. (17) were evaluating a possible antinociceptive synergistic interaction of metamizol (NSAID) and tramadol (an atypical opioid, opioid receptor agonist), when administered alone or in combination, as well as the possible development of pharmacological tolerance produced by such combination. The results of the study showed that both metamizol and tramadol produced antinociceptive effects with a low rate trend towards tolerance development at the end of the treatment. The antinociceptive efficacy of tested combination gradually decreased after the second injection. These data suggested that when the combination is given in a unique administration it results in an important potentiation of their individual antinociceptive effects. But, the repeated coadministration of tramadol and metamizol results in a development of tolerance.

The experimental part of our study presents the similar results. Application of individual substances lornoxicam and tramadol showed the expected results. Both, tramadol and lornoxicam produced a significant analgesic effect in applied doses, which was statistically different compared to the control group, for each method of application.

The combination of tramadol and lornoxicam, after i.p. application, produced increased pain reaction (enhanced antinociception) when compared to lornoxicam alone under the same conditions ($p < 0.05$). These results confirm the literature data on combining opioids and drugs from the group of NSAIDs.

Subcutaneous administration of tested combination showed some different results. Just in the first

observed time interval after application, the combination of tramadol and lornoxicam produced significantly better analgesic effect compared to lornoxicam alone ($p < 0.05$). At later time points (60, 90 and 120 minutes), the effect of this combination is almost the same as the effect of lornoxicam, thus, increased latency was demonstrated, but with no statistically significant difference.

CONCLUSIONS

After intraperitoneal administration, latency period of lornoxicam was increased as compared to the control group, with significant difference after 60, 90 and 120 minutes of test. Lornoxicam also showed increased latency when administered subcutaneously.

Lornoxicam significantly increases analgesic effect when applied intraperitoneally in combination with tramadol. On the other hand, lornoxicam in combination with tramadol, did not increase the threshold of sensitivity to painful stimuli with significant difference, after subcutaneous administration.

The findings of the combination that includes opioid and nonopioid reveal that it has potential for development as one of the new strategies of analgesics. Any clinical decision of using such multimodal approach in pain therapy, in addition to increasing the antinociception which has been experimentally demonstrated in our study, should also be based on the benefits coming from reduction of adverse effects of opioids in comparison to the side effects of non-opioids involved in such combination.

COMPETING INTERESTS

The authors declare no conflict of interest.

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