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The Antioxidative Property of Nitroglycerin Enhances Lornoxicam's Antiinflammatory Effect

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Abstract

Background and objectives: The aim of the study is to evaluate the effect of combination of nitroglycerin and lornoxicam on nociception and antioxidative system in rats.

Methods: Thirty-nine Wistar male rats were divided into five groups; control group (Group C, n=7), isotonic group (0.09 sodium chloride, Group ISO, n=8), lornoxicam group (lornoxicam 1.3 mg kg^{-1}, Group L, n=8), nitroglycerin group (nitroglycerin 1 mg kg^{-1}, Group N, n=8), and lornoxicam-nitroglycerin combination group (1.3 mg kg^{-1} lornoxicam+1 mg kg-1 nitroglycerin Group L+N, n=8). Hot plate test was applied in all groups before and at 30, 60, 90 minutes after drug injections by intraperitoneal route. Malondialdehyde, nitric oxide, glutathione, and catalase concentrations were measured before and after 90 minutes of drug injection in all blood samples.

Results: The latency response of hot plate test was increased in Group L+N at 30 minutes, and Group L and Group L+N at 60 and 90 minutes ($p<0.05$). Malondialdehyde levels were decreased, while catalase and glutathion levels were increased in N and L+N groups ($p<0.05$).

Conclusion: Nitroglycerin enhances the antioxidative effects of lornoxicam for antinociception but different mechanisms might also play a role on antinociception. Further studies must be carried out with experimental models and different drug doses to reach an ultimate conclusion.

Keywords: Nociception; NSAIDs; Lornoxicam; Nitroglycerin; Nitric oxide; Antioxidative enzymes

Introduction

Painful stimulation increases oxidative stress and the production of free radicals. Antioxidative therapy may be assisted to decrease the doses of analgesics on nociception [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in management of pain. The antinociceptive effect of NSAIDs is mainly due to their common property of inhibiting cyclooxygenases involved in the formation of prostaglandins.

Nitroglycerin (nitric oxide precursor) transdermal may reduce spinal or epidural analgesia requirements and augment analgesia to prolong time to first rescue analgesia administration postoperatively [2-4]. Antioxidative effect of nitroglycerin has been shown in many studies [5-7].

Nitric oxides releasing non-steroidal anti-inflammatory drugs are a new class of cyclooxygenase inhibitors designed to potentiate the release of nitric oxide. These drugs have been shown to exhibit greatly reduced gastrointestinal toxicity in animals and humans with anti-inflammatory and analgesic efficacy comparable or superior to the parent drugs [8].

Lornoxicam is a NSAID with a plasma half-life of 3 to 5 hours [9]. Although different NSAIDs have been combined with nitric oxide donors in previous studies, systemic administration of a mixture of lornoxicam and nitroglycerin has not been investigated on nociception to the best of our knowledge. The aim of this study is firstly, to investigate the effect of combination of nitroglycerin and lornoxicam on nociception and secondly, to determine the antioxidative effects of this combination in rats.

Material Methods

Animals: Male Wistar rats weighing approximately 300-450 g were obtained from Adnan Menderes University Medical Faculty of Animal Ressearch Labarotory Center (Aydin, Turkey). They were housed in polypropylene cages in groups of five per cage, and received standard laboratory chow and tap water ad libitum with 12/12 hours light/dark cycles. All experimental protocols were approved by Animal Ethics Committee of Adnan Menderes University Medical Faculty.

Drugs: Lornoxicam (Xefo®, Abdi Ibrahim, Istanbul, Turkey), and nitroglycerin (Perlinganit®, Adeka, Istanbul, Turkey) were used. Drug solutions were prepared so that the desired dose, expressed in terms of saline, was contained in a volume 10 ml kg^{-1} of body weight for intraperitoneal (i.p.) injection 30 minutes before nociceptive test.

Thirty-nine Wistar male rats were divided into five groups; control group (No drug was given to control group, Group C, n=7), isotonic group (0.09 sodium chloride, Group ISO, n=8), lornoxicam group (lornoxicam 1.3 mg kg^{-1}, Group L, n=8), nitroglycerin group (nitroglycerin 1 mg kg^{-1}, Group N, n=8), and lornoxicam-nitroglycerin combination group (1.3 mg kg^{-1} lornoxicam + 1 mg kg^{-1} nitroglycerin Group L+N, n=8).

Assessment of central nociception

Hot plate assay: In this test, animals were individually placed on a hot

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plate maintained at a constant temperature (56±0.3°C) (May Tic., Ankara). The latency to first sign of hind paw licking or jump response to avoid heat nociception was taken as an index of nociceptive threshold with cut off time of 60 seconds. The nociceptive threshold was observed before, and 30, 60 and 90 minutes after the drug administration.

Biochemical analysis

The blood samples were drawn an hour before and 90 minutes after the drug injection for the measurements of malondialdehyde, nitric oxide, glutathione, and catalase concentrations. Rats were sedated by ether anesthesia when the blood samples were drawn.

Blood samples were prepared for serum nitric oxide, catalase, and glutathione levels. Sera were obtained by centrifugation at room temperature and the samples were stored at -80°C until analysis.

Measurement of nitric oxide (nitrite+nitrate) level

Nitric oxide (NO) has a very short half-life in the serum. When nitric oxide is carried in the bloodstream, it is oxidized by erythrocytes and forms the stable end-products, nitrate (NO_3-) and nitrite (NO_2-), which provides an indirect measure of nitric oxide. The sum of nitrite and nitrate (NO_2- + NO_3-) has been confirmed to be a good indicator of nitric oxide production. In this study, nitrite and nitrate levels were analyzed using a modification of the cadmium-reduction method as described by Cortas and Wakid [10]. Nitrate (NO_3-) was reduced to nitrite (NO_2-) with cadmium granules and the nitrite concentration was then measured with the Griess reagent.

Preparation of hemolysates: Blood was collected into tubes containing citrate as anticoagulant. Blood samples were centrifuged at 3000 rpm 10 min at +4°C. The buffy coat on the erythrocyte sediment was separated carefully after the plasma was removed. The erythrocyte sediment was washed three times with 0.9 % NaCl solution to remove leftover leukocytes and plasma components. After each procedure, erythrocyte-saline mixture was centrifuged at 3000 rpm 10 min at +4°C. Erythrocyte sediments were treated with 4-fold ice-cold deionized water to obtain stock hemolysate containing ~5 g hb/100 ml.

Hemoglobin determination: Hemoglobin content of hemolysates was measured using GEN-S coulter haematology analyser.

Malondialdehyde (MDA) determination

Serum malondialdehyde concentration was measured as an indirect marker of oxidative stress in terms of thiobarbituric acid reactive substances, spectrophotometrically [11].

Serum samples (0.125 ml) were mixed with 20% trichloroacetic acid (1.25 ml) and 0.67% thiobarbituric acid (0.5 ml). Mixture was then boiled at 95°C for 30 minutes, immediately followed by cooling on ice. Reaction mixture was then vortexed, following the addition of n-Butanol (2ml). All vials were then centrifuged at 3000 rpm for 10 min. Absorbance of the supernatant was then measured at 535 nm. Concentration of lipid peroxidation products was calculated as malondialdehyde concentration using the extinction coefficient for malondialdehyde -thiobarbituric acid complex of 1.56×10^5 / mol/ cm.

Catalase enzyme activity

Catalase levels were measured in a fresh suspension of hemolysates. 1:1000 dilution of this concentrated homolysate was prepared with phosphate buffer immedialety before the assay catalase activity was determined by the method of Aebi [12].

Glutathione determination

Blood was collected into tubes containing EDTA as anticoagulant. Reduced glutathione level was estimated by the monitoring the reduction of DTNB (dithiobis-2-nitrobenzoic acid) forming a yellow coloured anion at 412 nm [13].

Statistical analysis

Statistics for analgesia: One way ANOVA, student's t test with Bonferroni correction was used to compare five groups at each time point. ANOVA with repeated measurements across time was used, followed by Dunnet's test.

Statistics for biochemical markers: Changes for each group were analyzed with paired t test. ANOVA with repeated measurements across time was used, followed by Bonferroni correction.

Results

Antinociceptive effects of drugs

There was significantly difference between the groups in hot-plate test at 30, 60 and 90 minutes after injection of the drugs ($p<0.001$). A significant increase was observed at 30 minute in Group L+N compared to other groups. The latency response in hot-plate assays was higher in Group L and Group L+N, compared to other groups at 60 minutes. At 90 minutes, the latency response in hot-plate assays was higher in Group L and Group L+N, compared to other groups. Significance levels of multiple comparison analysis for hot plate test between groups are shown in Table 1.

	Hot plate baseline	Hot plate 30 min	Hot plate 60 min	Hot plate 90 min
Group C	7.24±1.22	7.80±1.50	7.38±0.98	9.07±2.10
Group ISO	7.78±1.24	9.33±1.09	9.28±1.31	9.17±2.60
Group N	8.78±1.28	9.33±1.34	9.25±2.14	9.70±2.80
Group L	8.70±1.33	10.3±2.10	20.52±5.12▲	27.75±6.54■
Group L+N	7.86±1.42	21.25±3.4◆	28.20±5.30●	32.90±8.57★

Data are means ± SD.
▲ In Group L, compared to Group C (p= 0.006), Group ISO (p= 0.012), and Group N (p= 0.018), at 60 min.
■ In Group L, compared to Group C (p= 0.001), Group ISO (p= 0.001), and Group N (p= 0.001) at 90 min.
◆ In Group L+N, compared to Group C (p= 0.001), Group ISO (p= 0.001), Group N (p= 0.001), and Group L (p= 0.001) at 30 min.
● In Group L+N, compared to Group C (p<0.001), Group ISO (p<0.001), Group N (p<0.001), and Group L (p= 0.001) at 60 min.
★ In Group L+N compared to Group L (p= 0.007) at 90 min.

Table1: Changes in latency of hot plate test (seconds) at 30, 60, 90 minutes in groups.

	Nitric oxide levels (μmol/L)		Malondyaldehid levels (nmol/mL)	
	baseline value	after painful stimulation	baseline value	after painful stimulation
Group C	23.5±5.4	24.2 ±6.5	0.42±0.07	0.54±0.03
Group ISO	22.4±5.2	23.1±5.9	0.43±0.1	0.56±0.02
Group N	24.2±6.4	93.3±12.4▲	0.42±0.05	0.33±0.09◆
Group L	22.3±5.6	22.5±8.4	0.41±0.05	0.43±0.05
Group L+N	23.4±5.3	39.5±7.3	0.40±0.03	0.32±0.01■

Groups are presented as Group C (no drug was given), Group ISO (isotonic group), Group N (nitroglycerin group; 1 mg kg^{-1}), Group L (lornoxicam group; 1.3 mg kg^{-1}), Group L+N (nitroglycerin-lornoxicam combination group; 1.3 mg kg^{-1} lornoxicam+ 1 mg kg^{-1} nitroglicerin).
▲ In Group N, after painful stimulation compared to baseline values (p<0.001), for nitric oxide levels.
◆ In Group N (after painful stimulation) compared to Group C (p= 0.033), Group ISO (p= 0.036), for malondyaldehid levels.
■ In Group L+N (after painful stimulation) compared to Group C (p= 0.031), Group ISO (p= 0.028), for malondyaldehid levels.

Table 2: Changes in nitric oxide and malondialdehyde levels before drugs administration and after painful stimulation.

	Glutathione (μmol/g Hb)		Catalase (k/g Hb)	
	baseline value	after painful stimulation	baseline value	after painful stimulation
Group C	3.32±0.47	3.29±0.41	418.43±51.24	406.38±44.23
Group ISO	3.25±0.56	3.34±0.36	420.32±63.91	412.44 ±58.82
Group N	3.29±0.34	4.71±0.44▲	416.74±48.63	589.38±54.83*
Group L	3.43±0.38	3.82±0.42■	420.26±87.18	492.42±39.45●
Group L+N	3.33±0.45	5.52±0.24◆	421.34±75.96	687.36±62.75●

Data are means ± SD
▲After painful stimulation, in Group N, compared to Group C (p=0.0022), Group ISO (p=0.0028) and Group L (p=0.032) for glutathione levels.
■After painful stimulation, in Group L+N, compared to Group C (p<0.0001), Group ISO (p<0.0001), Group L (p<0.0001) and Group N (p=0.041) in for glutathione levels.
◆After painful stimulation, in Group L, compared to Group C (p=0.043), Group ISO (p=0.042), for glutathione levels.
*After painful stimulation, in Group N, compared to Group C (p=0.0024), Group ISO (p=0.0019) and Group L (p=0.028) for catalase levels.
●After painful stimulation, in Group L+N, compared to Group C (p<0.0001), Group ISO (p<0.0001) and Group L (p=0.005) for catalase levels.
●After painful stimulation, in Group L, compared to Group C (p=0.024) and Group ISO (p=0.022) for catalase levels.

Table 3: Changes in glutathione and catalase levels before drugs administration and after painful stimulation.

Biochemical results

There was no significant a difference for the baseline value (before drug injection) of nitric oxide, malondialdehyde, glutathione and catalase levels in all groups.

Nitric oxide levels was found high in only nitroglycerin group after painful stimulation compared to baseline value (p<0.001). The result of nitric oxide levels is summarized in Table 2.

Malondialdehyde levels decreased after painful stimulation compared to baseline values in Group N (21%) (p=0.039) and Group L+N (20%) (p=0.041). The result of malondialdehyde level is summarized in Table 2.

Glutathione levels increased after painful stimulation compared to baseline values in Group N (43%) (p= 0.0028) and Group L+N (65 %) (p<0.001).

After painful stimulation, there was significant difference between Group L+N, and others groups [Group C (p<0.0001), Group ISO (p<0.0001), and Group L (p<0.0001)] for glutathione levels.

Catalase levels also increased after painful stimulation compared to baseline values in Group L (17%) (p= 0.032), Group N (41%) (p= 0.0021) and Group L+N (63 %) (p<0.001).

After painful stimulation, there was significant difference between Group L+N, and others groups [Group C (p<0.0001), Group ISO (p<0.0001), and Group L (p=0.005)] for catalase levels.

Glutathione and catalase levels were also significantly different in Group N and Group L+N (p=0.041 and p= 0.043 for glutathione and catalase levels with respectively).

The results of glutathione and catalase levels are summarized in Table 3.

Discussion

The main result of our study was the finding that addition of nitroglycrine to lornoxicam enhances antinociceptive effects compared to lornoxiam alone in rats. Furthermore, nitroglycerin addition to lornoxicam increased antioxidative enzymes levels such as catalase and glutathione.

Nitroglycerin is a nitric oxide (NO) donor and this has been confirmed by the measurement of the NO levels in our study. It was demonstrated that the nitroglycerin treatment significantly enhanced plasma catalase, and glutathione-S-transferase (antioxydative enzymes) activities while decreasing malondialdehyde levels (as oxidative stress marker) in rats [6]. Sokolowska and collagues [7] also showed that the use of 2.5 mg kg^{-1} nitroglycerin administered by intraperitoneal route in rats for 5, 10 and 17 days, causes in antioxidant reactions without any hypotensive effects. Similarly, the use of nitroglycerin alone produced antioxidative effects that have been confirmed by the increase of glutathione and catalase levels in our study.

Painful stimulation increases oxidative stress and the production of free radicals which increase lipid peroxidation [1]. It was demonstrated that in patients with acute abdominal pain, the level of malondialdehyde increased and the level of total antioxidant capacity decreased [14]. Rokyta and colleagues suggest that the administration of antioxidants in pain treatment may be employed to decrease the doses of analgesics such as acetylsalicylic acid and to prevent the negative impact of reactive oxygen species on nociception, however, antioxidants alone are ineffective in pain treatment. The consequence of antioxidative effects is a blockade of the pain induced increase of malondialdehyde levels (as oxidative stress marker) which is observed in the use of nitroglycerin [1]. Antioxidative markers such as glutatahione and catalase levels were also increased in Nitroglycerin group compared to control group after painfully stimulation in our study.

Lornoxicam might also show antioxidative effects in rats [15]. Although lornoxicam alone moderately enhanced antioxidative enzymes, the highest antioxidative effects which were found in lornoxicam-nitroglycerin combination group in our study. It might be related to synergic effect between these drugs. In addition, nitric oxide level raise was higher in nitroglycerin group than the combination of nitroglycerin and lornoxicam group. This might be related to the pharmacokinetic interaction between nitroglycerin and lornoxicam. Similarly, administration of single dose of nitric oxide releasing NSAID in the rat allows the use of lower doses and plasma levels of NSAID for the same efficacy [16]. It may explain the improvement of lornoxicam-induced analgesia observed with the nitroglycerin in our study. We conclude that antioxidative and synergistic effects of nitroglycerin may increase the antinociceptive effect of lornoxicam.

We evaluated antinociceptive effects of drugs with hot plate test. This test is appropriate for the detection of antinociception that is mediated predominantly by central mechanism [17]. This test consists of introducing a rat or mouse into an open-ended cylindrical space with a floor consisting of a metallic plate that is heated by a thermode or a boiling liquid. A plate heated to a constant temperature produces two behavioral components that can be measured in terms of their reaction times, namely paw licking and jumping. Both are considered to be spinally and supraspinally integrated responses. The jumping reaction time is increased equally by less powerful analgesics such as acetylsalicylic acid or paracetamol [17]. Actually, it has been demonstrated that NSAIDs also have a direct action on spinal nociceptive processing that augments the peripheral mechanism, and correlates with their capacity as inhibitors of cyclooxygenase (COX) activity. In addition, it has been shown that prostaglandins (PGs), which are synthesized from arachidonic acid by COX, play an important role in the development of spinal hyperexcitability, and hyperalgesia. As is now generally accepted, COX exists as two distinct isoforms (COX-1 and COX-2), and both proteins are present in rat spinal cord. Several studies suggest that NSAIDs, through COX inhibition, may modulate the development of central hyperalgesia, and exert analgesic effects [18,19]. Lornoxicam produces inhibition of both COX-1 and COX-2 without a clear selectivity and may show central analgesic effect. We preferred the dose of 1.3 mg kg^{-1} for lornoxicam since it was found to be fully effective to prevent hyperalgesia in rats [19].

In the early 20th century, the role of NO was discovered in nociception both centrally and peripherally. There is no doubt that the pain treatment with NO donors started with nitroglycerine (NTG), one of the oldest available treatments for patients with ischaemic heart disease. The physiological effect of NTG as a potent vasodilator results after constitutive NOS activation and synthesis of NO, which is responsible for vasodilatation. It seems worthwhile to mention the effects of transdermal NTG in analgesia, including enhancing the anti-nociception from spinal administration of either sufentanil following orthopaedic surgery or neostigmine in acute post-operative pain, and acting as a co-adjuvant in opiate therapy for the control of cancer pain. Impaired NO generation may play a role in diabetic neuropathic pain as it was found that isosorbide dinitrate spray (ISDN), a NO donor with local vasodilating properties, relieved pain in a small number of patients with diabetic neuropathic pain [20]. Nitric oxide donors can also act as hyperalgesic or antihyperalgesic. Explanations for the discrepant results on the involvement of nitric oxide in nociceptive processing include drug specificity, dose, and route of administration, distribution, and pharmacokinetics [21]. Although subcutaneous L-arginine (0.3–1.0 mg kg^{-1}) reduced hyperalgesia, higher doses (600 mg kg^{-1}, i.v.) had no effect on pain or increased the carrageenan-induced hyperalgesia in the rat paw pressure test [22]. Therefore, we chose to add low doses (1 mg kg^{-1}) of nitroglycerin to lornoxicam for analgesic effect.

The latency response in hot plate test was higher when the use of lornoxicam and nitroglycerin together, but not the use of nitroglycerin alone. Similar to our results, low doses of transdermal nitroglycerin in humans (5 mg) alone did not have analgesic effects, but it enhanced analgesic effect of NSAIDs when used for shoulder pain due to supraspinatus tendonitis or as coadjuvant for spinal anesthesia [20,23]. We previously suggested that low dose nitroglycerine when added to lidocaine in intravenous regional anesthesia decreased postoperative analgesic requirement [24].

NO is implicated in the regulation of COX activity and activates COX, followed by an increase in prostaglandin synthesis. NO mediates several of its beneficial effects, such as maintenance of blood vessel tone, inhibition of platelet aggregation and cytoprotection, through the activation of COX. The discovery of the reciprocal interaction between NO/COX has opened up the possibility of designing new drugs, with a better toxicological and safety profile, containing NO donors conjugated with COX inhibitors [20].

The rationale for the enhanced antinociceptive activity of nitric oxide releasing NSAID is not clear. Nitric oxide-paracetamol pretreatment of rats reduced action potential and `wind-up' in dorsal horn neurons [25]. Nitric oxide also causes an increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP), which produces pain modulation in central and peripheral nervous system [6]. In present study we thought that the antioxidative and synergistic effects of nitroglycerin may increase the antinociceptive effect of lornoxicam.

The limitation of this study is that there is no group with different doses of lornoxicam and nitroglycerin. We believe further studies should be focused on including isobolgraphic analysis of these drugs combination.

We concluded that co-administration of nitroglycerin and lornoxicam might enhance antinociceptive effects compared to lornoxicam administration alone in rats. We may interpret this result as nitroglycerin increases antioxidative effects of lornoxicam beside other many mechanisms which play role on antinociception. Further studies must be carried out with experimental models and different drug doses to reach an ultimate conclusion.

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