

Effects of Dexamethasone, Clonidine, Tramadol and Nalbuphine on Fentanyl-Induced Hyperalgesia in Rats

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Abstract

Opioids are drugs used to alleviate pain. However, studies have demonstrated that these drugs can cause an increase in pain sensitivity, which is called opioid-induced hyperalgesia. The objective of this study was to describe the effects of dexamethasone, clonidine, tramadol and nalbuphine on fentanyl-induced hyperalgesia in rats. After obtaining approval from the Committee for the Ethical Use of Animals (CEUA), 36 male Wistar rats were divided into 6 groups: Group 1 (GCSSL) wherein the rats received 1 ml 0.9% saline solution in two injections; Group 2 (GFTSL), received fentanyl at a dose of 100 $\mu\text{g}\cdot\text{kg}^{-1}$ followed by 1 ml 0.9% saline solution via intraperitoneal; the remaining groups (3, 4, 5, 6) received fentanyl at a dose of 100 $\mu\text{g}\cdot\text{kg}^{-1}$ following doses via intraperitoneal: Group 3 (GFTDX), dexamethasone at a dose of 1.0 $\text{mg}\cdot\text{kg}^{-1}$; Group 4 (GFTCL), clonidine at a dose of 20 $\text{mg}\cdot\text{kg}^{-1}$; Group 5 (GFTTR), tramadol at a dose of 50 $\text{mg}\cdot\text{kg}^{-1}$, and Group 6 (GFTNB), nalbuphine at a dose of 5 $\text{mg}\cdot\text{kg}^{-1}$. Under general anesthesia using isoflurane, the animals were submitted to a surgical incision. Hyperalgesia was evaluated by applying Von Frey filaments at 2 hours after the incision and on the 1st, 3rd and 5th days afterward. At 2 hours after the surgical procedure, there was lower intensity of pain in the fentanyl group (GFTSL) compared to the other groups, and on the fifth day there were no significant differences for pain intensity between groups. The results suggest the presence of fentanyl-induced hyperalgesia and efficacy in its reduction by dexamethasone, clonidine, tramadol and nalbuphine.

Keywords

Hyperalgesia, Fentanyl, Dexamethasone, Clonidine, Tramadol, Nalbuphine, Rats

1. Introduction

Pain is one of the most important and complex human experiences and is defined by the International Association for the Study of Pain (IASP) as “disagreeable sensory or emotional experience associated with real or potential bodily injury” [1].

The use of opioids for pain treatment has increased in during recent years, and in some countries, they have become the most commonly prescribed drugs [2]. However, this increase has created problems such as abusive use, and several diverse events including fentanyl-induced hyperalgesia, a phenomenon wherein, paradoxically, the opioid can induce or make patients more sensitive to sharp pain [3] [4] [5]. In this situation, patients that receive opioids may experience significant post-operative sharp pain, thus causing greater tolerance to increasing doses and subsequent anxiety expressed by the patient as well as the doctor [4].

Among the supposed mechanisms responsible for hyperalgesia induced by opioids (HIO) are alterations in the N-methyl-D-aspartate (NMDA) receptors and secondary messengers, activation of spinal cyclooxygenase (COX), liberation of excitatory amino acids, reduction of inhibitory neurotransmitters, descending facilitation, and the anti-analgesic system [2] [3] [6].

The increased in the liberation of glutamate in the dorsal horn of the spinal cord and the subsequent maintained increase in the stimulus and response of NMDA receptors due to the removal of magnesium mediated by protein kinase C seem to be the principal mechanisms involved in HIO [7].

These NMDA receptors can be activated by opioids, which act as excitatory neurotransmitters causing an increase in calcium in the cell and centralized sensitivity. The entry of calcium into the cell provokes an increase in the activity of protein kinase C, phosphorylation, and inactivation of opioid receptors, besides causing an increase in nitric oxide synthase [8].

HIO has been associated with an increase in cholecystokinin, for a peptide related to the gene calcitonin (CGRP), substance-P, and nociceptin in the rostral ventromedial medulla due to increase in expression of excitatory opioid receptors, in detriment inhibitory opioid receptors [9] [10] [11].

The descending facilitation pathways, mediated by opioids and located in the rostral ventromedial medulla, are also involved in HIO due to neuroplastic [12], since exposure to morphine causes neuroplastic alterations in the rostral ventromedial medulla with an increase in the liberation of dynorphin and neurotransmitters of primary afferent fibers [3]. In this context, the administration of an opioids causes an increase in dynorphin, which can favor HIO [9] [13].

There is evidence that spinal dynorphin is pronociceptive, causing liberation of excitatory neurotransmitters of primary afferent neurons, suggesting a positive feedback, thus amplifying sensitive afference [13]. Furthermore, prostaglandins, cytokines, and chemokines can also be relevant to the development of HIO since opioids activate the liberation of cytokines and cause an increase in c-FOS protein in sensitive neurons in the medulla. Another system that could be involved in HIO is the nitric oxide synthase system, along with hemoxygenase, which could reduce glycinergic inhibitory control [2] [3].

Among the steroidal anti-inflammatory drugs, some prevent sensitivity to nociceptors through inhibition of the phospholipase A2, and therefore of the entire cascade of arachidonic acid, inhibiting COX-1 as well as COX-2. These drugs appear to have a relevant role in inhibition of hyperalgesia through stimulation and recapture of glutamate in the dorsal horn of the spinal cord, besides blocking NMDA receptors, with dexamethasone having a smaller mineralocorticoid effect than other drugs in this group [3] [14].

Studies have examined the role of agonists of the $\alpha 2$ receptor in the modulation of HIO, and have shown that clonidine attenuated post-infusion hyperalgesia induced by opioids and eliminated secondary post-infusion hyperalgesia induced by opioids, suggesting participation of $\alpha 2$ receptors in the modulation of HIO [15].

Tramadol is an example of an analgesic that demonstrates multiple mechanisms of analgesic action through the combined action of the enantiomers of the original drug and the enantiomers of its metabolite O-desmethyl (M1), which has at least three mechanisms: affinity for the morphine opioid receptor, inhibition of neuronal recapture of norepinephrine, and inhibition of neuronal recapture of serotonin, and since these are chemically modified, they have a strong analgesic effect. In this sense, it has been suggested that tramadol could be useful in the prevention of HIO [16].

Nalbuphine is a agonist of the kappa (κ) opioid receptor and na antagonist of the mi (μ) receptor, which acts as a weaker analgesic, but which can retard or inhibit tolerance to morphine, besides inhibiting HIO [17].

In this sense, this study used adjuvants commonly used in anesthetic procedures, including the steroidal anti-inflammatory drug—dexamethasone, alpha2-adrenergic agonist—clonidine, opioid agonist—tramadol and the opioid agonist-antagonist—nalbuphine.

2. Objective

Describe the effects of the drugs: dexamethasone, clonidine, tramadol and nalbuphine on fentanyl-induced hyperalgesia in rats using a standard plantar surgical incision.

3. Material and Methods

3.1. Animals

A total of 36 male Wistar rats weighing between 220 and 300 grams was allo-

cated in compartments in groups of six. The rats remained in these compartments for 15 days before the start of the experiment to adapt to the confined environment and were fed a nutritionally balanced commercial feed and water “*ad libitum*”, and were subjected to a 12-hour light-dark cycle with ambient temperature varying between 19°C and 25°C.

3.2. Ethical Aspects

The experimental procedures followed the ethical standards of the *International Association for the Study of Pain* (IASP), which establishes the norms for animal experimentation (*Committee for Research and Ethical Issues of the IASP*), and the study began only after having received approval from the Committee for the Ethical Use of Animals Use (CEUA) of Taubaté University, under protocol (n°03/2017). All experiments were conducted in the Pharmacology Laboratory of the university.

3.3. Anesthetic Induction

To induce light anesthetic induction, the animals were placed in a 15 × 25 × 15 cm transparent glass chamber with a transparent lid in order to observe the animals, and the chamber had an opening on the top and the bottom for entry and exit of oxygen (O₂), anesthetic gases, and carbon dioxide.

The halogen agent used for anesthetic induction was isoflurane (Isoforine[®], Cristália, Itapira, Brazil), at a concentration of 4.0% in a 1.0 oxygen inspired fraction (FiO₂) of 1.0, administered using a calibrated vaporizer (HB Hospitalar) and maintained for 3 minutes, the time necessary so that the animal demonstrated loss of postural reflexes and inability to move within the chamber. Subsequently, the animal was removed from the chamber and positioned with the snout in a mask through which it continually received at 4% isoflurane in O₂, as was done in the chamber where anesthesia was induced.

3.4. Surgical Incision

The surgical procedure consisted of a 1.0 cm longitudinal incision on the right posterior paw, according to the post-operative pain model as described [18].

The incision was done using a scalpel with a number 11 blade, incising the skin and fascia the plantar of the paw, starting at 0.5 cm from the edge of the calcaneus and extending in the direction of the toes. Subsequently, the plantar muscle was elevated and longitudinally incised, with its insertion remaining intact. After hemostasis with light pressure on the surgical incision, all the planes were approximated and stitched with two separate stitches using needled thread *mononylon* 4-0.

3.5. Experimental Design

The animals were randomly divided into six groups (n = 6) and received equal volumes of drugs or 0.9% saline solution.

In group 1 (GCSSL) the rats received 1 ml 0.9% saline solution in two injec-

tion via intraperitoneal (IP). Group 2 (GFTSL) received fentanyl at a dose of 100 $\mu\text{g}\cdot\text{kg}^{-1}$ followed by 1 ml 0.9% saline solution via IP. The remaining groups (3, 4, 5, 6) received IP, fentanyl at a dose of 100 $\mu\text{g}\cdot\text{kg}^{-1}$ and the following doses via IP: Group 3 (GFTDX), dexamethasone at a dose of 1.0 $\text{mg}\cdot\text{kg}^{-1}$; Group 4 (GFTCL), clonidine at a dose of 20 $\text{mg}\cdot\text{kg}^{-1}$; Group 5 (GFTTR), tramadol at a dose of 50 $\text{mg}\cdot\text{kg}^{-1}$, and Group 6 (GFTNB), nalbuphine at a dose of 5 $\text{mg}\cdot\text{kg}^{-1}$.

3.6. Mechanical Hyperalgesia

The evaluation of hyperalgesia was done by applying von Frey filaments as conducted [18]. For the von Frey test, the animals were placed in a wooden chamber, with a floor of 0.5 cm checkered galvanized screen. A mirror was fixed to this floor so that the researchers could observe the application of the filament and the reflex of the member.

Before the application of the filaments the animals were maintained in the wooden chambers for about 15 minutes so they could adapt to the surroundings.

Each of the filaments, in decreasing order of pressure was applied three consecutive times with at intervals of 3 to 5 seconds, and a positive response was considered to be when the animal removed the incised member from the floor when the filament as applied.

When the animals had the incised member completely removed from the floor the value of pressure was registred as zero, meaming that no stimulus was necessary for the animal to remove its member from contact with the floor.

The data were registered on separate tables for each animal at 2 hours, and 1, 3 and 5 days after the surgical procedure and administration of the treatments. After evaluation of hyperalgesia the animals were euthanized through injection with sodium pentothal at a dose of 100 $\text{mg}\cdot\text{kg}^{-1}$.

3.7. Statistical Analysis

Statistical analysis was done using the software JMP[®] from the Statistical Analysis System (SAS) Institute, using analysis of variance (ANOVA) followed by student's t-test comparing each pair at a probability level of $\alpha = 5\%$.

4. Results

There was no statistical difference for the mean weight of animals between groups ($p > 0.05$).

Pain intensity and standard deviation, assessed using the von Frey filaments in all studied groups and moments, is show in **Table 1** and **Figures 1-4**.

At the second hour after the surgical procedure the pain intensity evaluated using the von Frey filaments is shown in **Figure 1**, showing a significant difference with a lower intensity of hyperalgesia in the group that received fentanyl (GFTSL) compared to the other groups.

At day one after the surgical procedure, pain intensity, as evaluated by the von Frey filaments, is shown in **Figure 2**, showing a significant difference with greater

hyperalgesia in the group that received fentanyl (GFTSL) compared to the other groups.

Table 1. Pain intensity and standard deviation, using the von Frey filaments in the groups.

Groups	2 nd hour		1 st day		3 rd day		5 th day	
	Means	SD	Means	SD	Means	SD	Means	SD
GCSSL	2.93	0.47	3.98	0.64	4.37	0.43	4.66	0.56
GFTSL	4.04	0.39	2.68	0.69	2.88	0.47	4.71	0.44
GFTDX	3.37	0.63	4.93	0.19	4.86	0.62	5.09	0.50
GFTCL	2.81	0.36	4.25	0.70	5.20	0.67	5.22	0.45
GFTTR	3.02	0.40	5.22	0.32	5.50	0.31	5.31	0.49
GFTNB	2.76	0.29	4.37	0.43	5.15	0.45	5.06	0.45

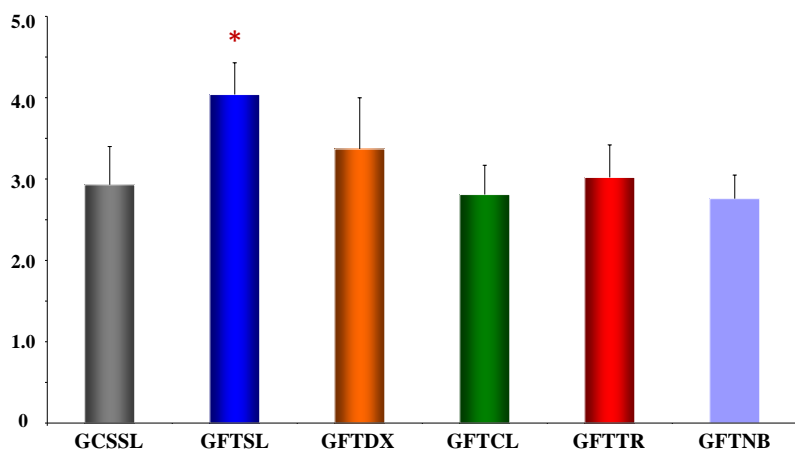


Figure 1. Pain intensity at the second hour after the surgical procedure for the groups: GCSSL, GFTSL, GFTDX, GFTCL, GFTTR and GFTNB. Student's t-test showing a significant difference compared to the fentanyl group (GFTSL*) compared to other groups ($p < 0.05$).

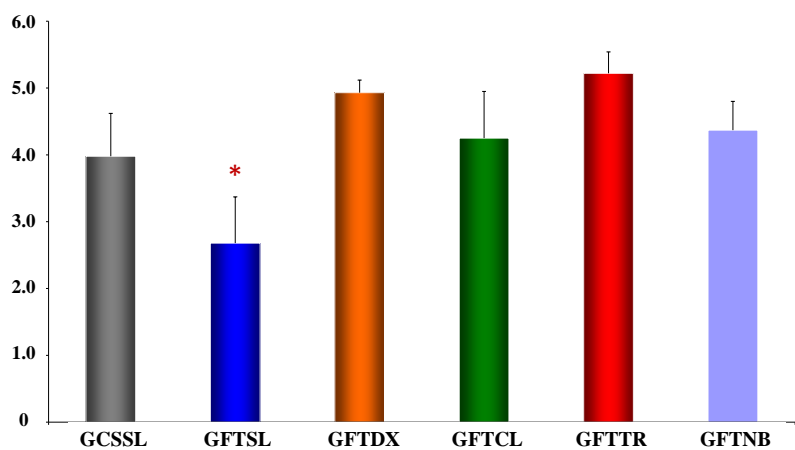


Figure 2. Pain intensity at the first day after the surgical procedure for the groups: GCSSL, GFTSL, GFTDX, GFTCL, GFTTR and GFTNB. Student's t-test showing a significant difference compared to the fentanyl group (GFTSL*) compared to other groups ($p < 0.05$).

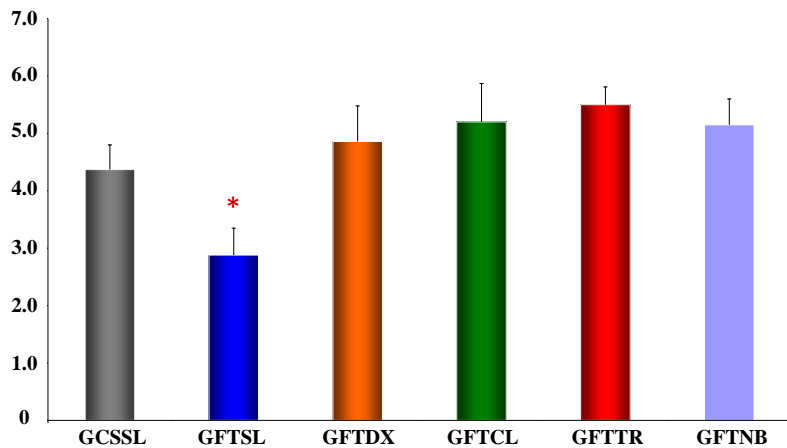


Figure 3. Pain intensity at the three day after the surgical procedure for the groups: GCSSL, GFTSL, GFTDX, GFTCL, GFTTR and GFTNB. Student's t-test showing a significant difference compared to the fentanyl group (GFTSL*) compared to other groups ($p < 0.05$).

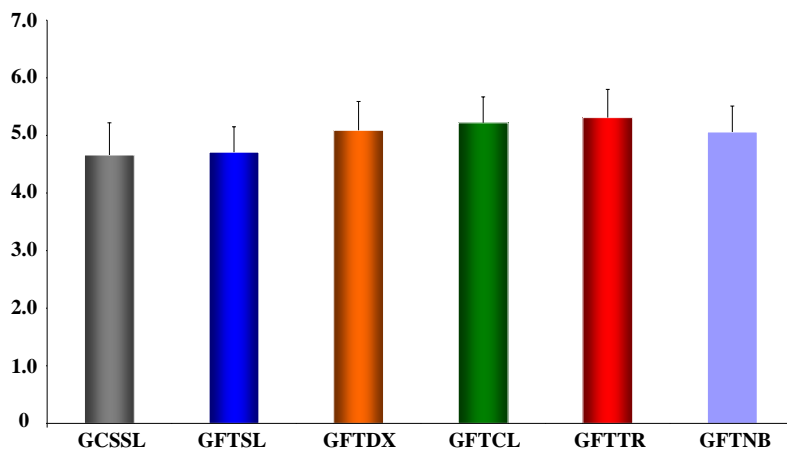


Figure 4. Pain intensity at the fifth day after the surgical procedure for the groups: GCSSL, GFTSL, GFTDX, GFTCL, GFTTR and GFTNB. Student's t test showing no significant differences between groups ($p > 0.05$).

At day three after the surgical procedure, as in day one, pain intensity, as evaluated by the von Frey filaments, is shown in **Figure 3**, showing a significant difference with greater hyperalgesia in the group that received fentanyl (GFTSL*) compared to the others groups.

At day fifth after the surgical procedure, pain intensity, as evaluated by the von Frey filaments, is shown in **Figure 4**, showing no significant differences with the other groups.

When the fentanyl-treated group was compared with the other groups, there was a significant difference in time points; 2nd hour, with less pain intensity, evaluated by von Frey filaments in the fentanyl group, probably due to its acute analgesic effect, is shown in **Table 2**.

However, on the 1st and 3rd day there was greater pain intensity in the group that received fentanyl alone, suggesting opioid-induced hyperalgesia and pain

Table 2. Comparative analysis between the group treated with fentanyl and the groups treated with saline solution and anesthetic adjuvants; dexamethasone, clonidine, tramadol and nalbuphine at the studied times.

Groups	2 nd hour	1 st day	3 rd day	5 th day
	P	P	P	P
GFTSL × GCSSL	0.0015	<0.0001	<0.0001	0.6431
GFTSL × GFTDX	0.0487	<0.0001	<0.0001	0.0603
GFTSL × GFTCL	0.0005	<0.0001	<0.0001	0.0594
GFTSL × GFTTR	0.0033	<0.0001	<0.0001	0.0507
GFTSL × GFTNB	0.0003	<0.0001	<0.0001	0.0743

There were significant differences between the fentanyl group (GFTSL*) and the other groups, in the 2nd hour, 1st and 3rd days afterward ($p < 0.05$). On the 5th day, there were no significant differences.

reduction when the animals received the drugs used as adjuvants in anesthesia, suggesting hyperalgesia attenuation with the use of these drugs.

5. Discussion

Opioids are medicines that are fundamental to pain treatment, however, while at the beginning of treatment they are considered analgesics and anti-hyperalgesics, they can posteriorly provoke hyperalgesia, thus making the patient more sensitive to pain [2] [9].

Opioid-induced hyperalgesia has been attributed to acute desensitization of receptors due to the derailment of the G protein of the opioid receptors, and activation of N-methyl-aspartate receptors, among other mechanisms [2].

Studies have shown that the concomitant use of low doses of opioid antagonists and antagonists of NMDA receptors can prevent or reduce development of HIO and that ketamine in low doses can modulate HIO [7] [19] [20].

Furthermore, it has been shown that mechanisms implicated in the development of HIO include the glutamatergic system and NMDA receptors, activation of spinal COX, excitatory amino acids, dynorphins, cytokines and chemokines, prostaglandins, and descending facilitation [6]. In this context, it can be conjectured that the modulation of hyperalgesia could be mediated by antagonists of NMDA receptors, alpha-2 adrenergic agonists, selective inhibitors of recapture serotonin, inhibitors of cyclooxygenases, analogous to GABA, and antagonists of μ opioid receptors [6] [21].

In this study, at the second hour after the surgical procedure, there was a greater analgesic effect in the group that received phenethyl, which can be explained by the more intense analgesic property of this drug [22].

When the animals were evaluated on the first and third day after the surgical procedure, the group that received fentanyl via IP showed a greater hyperalgesic effect with a significant statistical difference compared to the other groups that received fentanyl, and the drugs proposed in the study, thus demonstrating the

possibility of opioid-induced hyperalgesia and antihyperalgesic effect of the drugs used in this study.

It is important to emphasize that the control group, although it did not show a hyperalgesic effect as did the animals in the fentanyl group, did not receive fentanyl, and probably did not develop HIO and therefore did not obtain the analgesic benefits provided by the opioid.

On the fifth day after the surgical procedure, there were no statistical differences between groups, meaning that there was no residual effect of hyperalgesia induced by a single dose of fentanyl. Even so, a reduction in algesic sensitivity was observed for all groups compared to the evaluations at 2 hours and days 1 and 3, thus indicating possible conclusion of the algesic process.

6. Conclusion

The results obtained of this study suggest hyperalgesia induced by fentanyl and a possible attenuating effect mediated by the drugs dexamethasone, clonidine, tramadol and nalbuphine, and future studies should be conducted to further confirm and expand upon these findings.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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