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Effects of Ketoprofen, Ketamine, Lidocaine and Propofol on Fentanyl-Induced Hyperalgesia in Rats

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Abstract

Opioid-induced hyperalgesia negatively affects physiological pain management and presents a complex causal mechanism, involving, pharmacodynamic and pharmacokinetic factors of interactions with receptors, opioid-independent ascending systems and with pro-nociceptive systems. After approval by the CEUA, 42 male Wistar rats were divided into 7 groups: In group 1 (GCSSL) the animals received 1 ml of 0.9% saline solution intraperitoneally (IP); in group 2 (GFTSL), they received fentanyl at a dose of 100 ug·kg^{-1} IP; in the remaining groups (3, 4, 5, 6 and 7) the animals received IP, fentanyl at a dose of 100 ug·kg^{-1} followed also by IP route of: group 3 (GFTKP) ketoprofen at a dose of 5 mg·kg^{-1}; group 4 GFTKT), ketamine up to a dose of 10.0 mg·kg^{-1}; group 5 (GFTLI), incisional lidocaine up to a dose of 10 mg·kg^{-1}; group 6 (GFTLP), intraperitoneal lidocaine up to a dose of 10 mg·kg^{-1} and group 7 (GFTPP), propofol up to a dose of 60 mg·kg^{-1}. Under general anesthesia, all animals with a plantar surgical incision. Hyperalgesia was evaluated by applying Von Frey filaments on the 2nd, 1st, 3rd and 5th days after treatment. In the 2nd hour and on the 5th day after the procedure, there was no hyperalgesia associated with the use of fentanyl, however, on the 1st and 3rd postoperative days there was hyperalgesia that was attenuated by ketoprofen, ketamine, lidocaine infiltrated in the incision and intraperitoneally, an effect not observed with the use of propofol. The results suggest

fentanyl-induced hyperalgesia and the efficacy of ketoprofen, ketamine, incisional lidocaine and intraperitoneal lidocaine in reducing this effect.

Keywords

Hyperalgesia, Fentanyl, Ketoprofen, Ketamine, Lidocaine, Propofol, Rats

1. Introduction

The main side effect of the chronic use of opioids is tolerance, a phenomenon in which exposure to opioids leads to a reduction in analgesic potency, requiring higher doses to obtain the same therapeutic result 1. This effect occurs by desensitization of the antinociceptive pathway and reduction of membrane receptors by internalization. Another phenomenon observed more recently is the increased sensitization of the antinociceptive pathway described as Opioid-Induced Hyperalgesia [1].

Opioid-induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization due to exposure to opioids, in which, paradoxically, a patient receiving opioids to treat becomes more sensitive to certain painful stimuli [1] [2].

The occurrence of OIH can delay timely discharge and cause discomfort not only through higher pain scores, but also through increased use of analgesics and effects related to their administration [2].

The OIH is often confused with opioid tolerance and withdrawal-associated hyperalgesia, however, they are different phenomena that can manifest similar symptoms, but they must be differentiated from each other, since the treatment for each syndrome is different [1] [2] [3].

Among the putative mechanisms responsible for OIH are alterations of NMDA and second messenger receptors, activation of spinal COX, release of excitatory amino acids, reduction of inhibitory neurotransmitters, descending facilitation and the anti-analgesic system [1]-[6]. These mechanisms lead to neuroplastic changes in the central and peripheral nervous system with sensitization of nociceptive pathways [6].

The increased release of glutamate in the dorsal horn, from the spinal cord, triggered by opioids and the consequent activation of NMDA receptors, seems to be the main mechanisms implicated in OIH [7] [8].

There is evidence that spinal dynorphin is pronociceptive, causing the release of excitatory neurotransmitters from primary afferent neurons, suggesting positive feedback, amplifying sensory input [6]. In addition, prostaglandins, cytokines and chemokines may also be relevant in the development of OIH, as opioids activate the release of cytokines, with an increase in C-foz protein in spinal cord sensory neurons [8].

Tissue damage triggers activation of membrane phospholipases (A2 and C) leading to lysis of phospholipids giving rise to arachidonic acid, leading to pro-

duction of COX-1, COX-2, lipoxygenases and production of prostaglandin [9].

Opioids, such as fentanyl and its derivatives like sufentanil, remifentanil and alfentanil, are used in the induction and maintenance of general anesthesia. Fentanyl is a μ-opioid receptor agonist, was first synthetized in 1960 and clinical effect is 5 - 100 times stronger than that of morphine. It is widely used because of its rapid onset, short acting time, dose-dependent analgesic action, high cardiovascular stability and minimal histamine release [10] [11].

The inhibition of prostanoids synthesis is the subject of several studies that to the development of acetylsalicylic acid, acetaminophen and several NSAIDs. Although all of these agents have anti-inflammatory, antipyretic and analgesic properties, there are marked distinctions between the agents. A systematic review and meta-analysis comparing ketoprofen with other NSAIDs found that ketoprofen was the most effective [12].

Rapid onset of analgesic action is an important factor in prescribing for analgesia. In a study evaluating the speed of onset of several NSAIDs in toothache, ketoprofen 25 mg had an onset of action in approximately 30 minutes, while 50 mg od diclofenac had a latency of 60 minutes, 100 mg of tramadol had an onset of action in 120 minutes and 20 mg piroxicam, 120 minutes [13] [14] [15] [16].

Ketamine, an NMDA receptor antagonist, in addiction to potentiating opioid-induced analgesia, has demonstrated a suppressive effect on rebound hyperalgesia observed the day opioid infusion [8].

The benefits of using local anesthetics by various routes include analgesia, anti-hyperalgesia and anti-inflammatory properties through multiple mechanisms, including suppression of nerve impulse transmission through the dorsal root ganglion of intact or damaged peripheral nerves, attenuation of peripheral neurogenic inflammation, suppression of granulocyte and lysosome activity, reduced cytokine activity and suppression of central sensitization [17].

The propofol is a hypnotic derived from phenol, described for the first time in 1977, which for presenting; rapid induction and elimination, short duration of action, smooth recovery from anesthesia, few adverse effects, and no teratogenic and mutagenic effects, it is currently widely used in different contexts, but mainly in anesthetic induction and maintenance of total intravenous anesthesia [18]. Due to its inhibitory effect on NMDA receptors, propofol has properties in the attenuation of hyperalgesia, with a reduction in postoperative consumption of opioids and attenuation in the visual analog scale [19] [20].

In this sense, this research is justified by the possibility of fentanyl producing hyperalgesia that can be interfered with by drugs such as ketoprofen, ketamine, lidocaine and propofol.

2. Objective

Describe the effects of the drugs: ketoprofen, ketamine, incisional lidocaine, intraperitoneal lidocaine and propofol on fentanyl-induced hyperalgesia in rats using a standard plantar surgical incision.

3. Material and Methods

3.1. Animals

A total of 42 male Wistar rats weighing between 220 and 300 grams were allocated in compartments in groups of seven.

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 (*Commitee 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 chambre had an opening on the top and the bottom for entry and entry and exit of oxygen (O_2), 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 (FiO_2) 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 O_2, 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 [21].

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 seven 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 injections via intraperitoneal (IP). Group 2 (GFTSL) received fentanyl at a dose of 100 ug·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 ug·kg^{-1} and the following doses via IP: Group 3 (GFTKP), ketoprofen at a dose of 5.0 mg·kg^{-1}; Group 4 (GFTKT), ketamine up to a dose of 10 mg·kg^{-1}; Group 5 (GFTLI), incisional lidocaine up to a dose of 10 mg·kg^{-1}; Group 6 (GFTLP), intraperitoneal lidocaine up to a dose of 10 mg·kg^{-1} and Group 7 (GFTPP), propofol up to a dose of 60 mg·kg^{-1}.

3.6. Mechanical Hyperalgesia

The evaluation of hyperalgesia was done by applying Von Frey filaments as conducted [21]. 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 registered as zero, meaning 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 mg·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 Pain Intensity and standard deviation, assessed using the von Frey filaments in all study groups and moments, is shown in **Table 1** and **Figure 1-4**.

At the second hour the surgical procedure the pain intensity evaluated using

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

Groups	2nd hours		1st day		3rd day		5th day	
	Means	SD	Means	SD	Means	SD	Means	SD
GCSSL	2.93	0.47	3.97	0.33	4.37	0.15	4.32	0.22
GFTSL	4.04	0.46	2.68	0.33	2.89	0.29	4.72	0.43
GFTKP	5.90	0.83	4.90	0.34	4.35	1.37	4.88	0.87
GFTKT	5.13	0.46	5.40	0.37	4.97	0.51	4.84	0.40
GFTLI	5.97	1.06	4.53	1.16	4.43	0.27	4.69	0.54
GFTLP	6.04	0.63	5.38	1.23	5.25	1.05	4.66	0.96
GFTPP	3.12	0.52	3.09	0.40	3.69	0.76	4.99	0.23

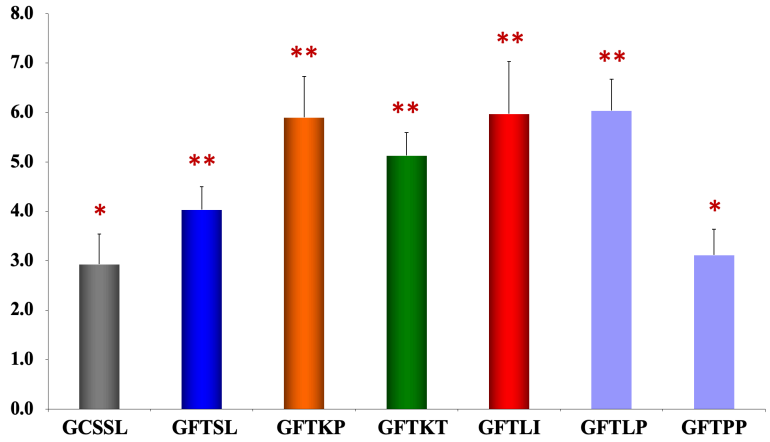

Figure 1. Pain intensity at the second hour after the surgical procedure for the groups: GCSSL, GFTSL, GFTKP, GFTKT, GFTLI, GFTLP and GFTPP. Student's t-test showed no significant difference when comparing GCSSL* with GFTPP* ($p = 0.6276$) but with statistical significance when comparing these with GFTSL**, GFTKP**, GFTKT**, GFTLI** and GFTLP** ($p < 0.05$).

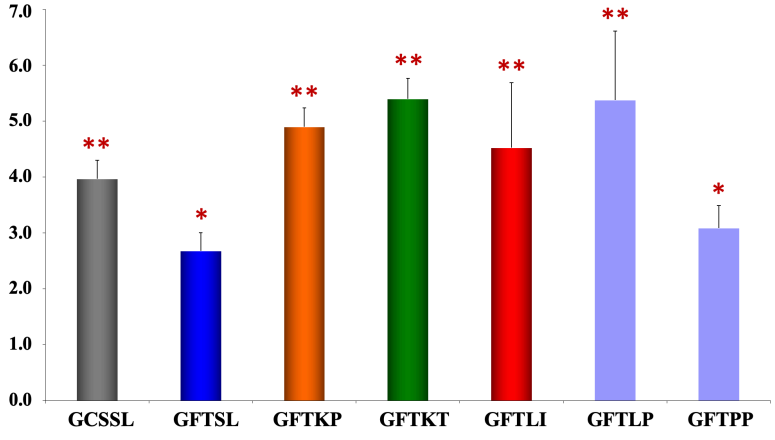

Figure 2. Pain intensity at the first day after the surgical procedure for the groups: GCSSL, GFTSL, GFTKP, GFTKT, GFTLI, GFTLP and GFTPP. Student's t-test showed significant difference when comparing GFTSL* with GCSSL**, GFTKP**, GFTKY**, GFTLI** and GFTLP ($p < 0.05$), but with no statistical significance when comparing these with GFTPP* ($p = 0.3611$).

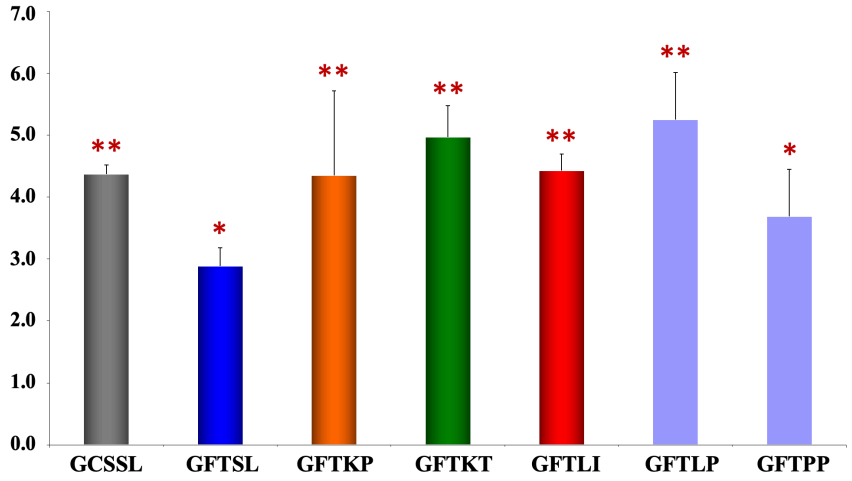

Figure 3. Pain intensity at the three day after the surgical procedure for the groups: GCSSL, GFTSL, GFTKP, GFTKT, GFTLI, GFTLP and GFTPP. Student's t-test showed significant difference when comparing GFTSL* with GCSSL**, GFTKP**, GFTKY**, GFTLI** and GFTLP ($p < 0.05$), but with no statistical significance when comparing these with GFTPP* ($p = 0.0758$).

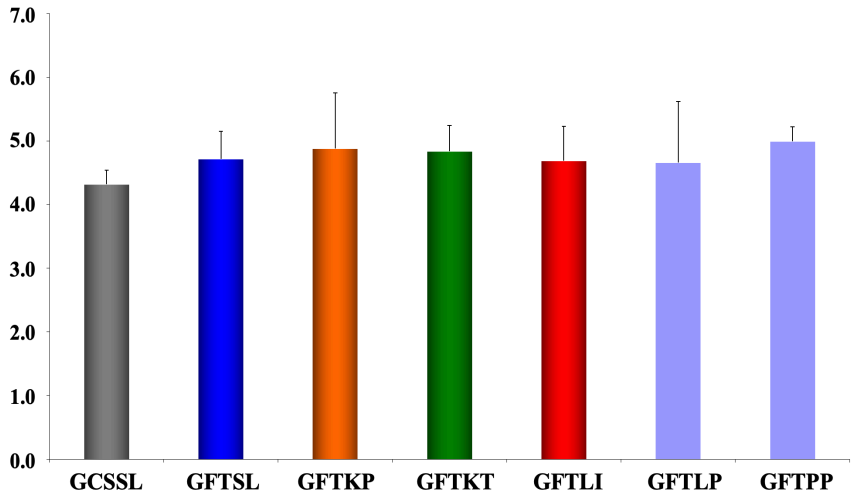

Figure 4. Pain intensity at the three day after the surgical procedure for the groups: GCSSL, GFTSL, GFTKP, GFTKT, GFTLI, GFTLP and GFTPP. Student's t-test showed no significant difference when comparing GFTSL with all other groups ($p > 0.05$).

the Von Frey filaments is shown in **Figure 1**, showing no significant difference when comparing with the GFTPP group, but with statistical significance of this the GFTKT, GFTKT, GFTLI and GFTLP groups.

At day one the surgical procedure the pain intensity evaluated after using the Von Frey filaments is shown in **Figure 2**, showing a significant difference between the GFTSL and the GFTKP**, GFTKT, GFTLI** and GFTLP** groups, but not with the GFTPP group.

On the third day after the surgical procedure, pain intensity, assessed by von Frey filaments, is shown in **Figure 3**, it did not show a significant difference between GFTSL with GFTPP, but significant when comparing GFTSL with the

GFTKP, GFTKT, GFTLI and GFTLP groups.

On the fifth day after the surgical procedure, the pain intensity, assessed by the von Frey filaments, shown in **Figure 4**, showed no difference between the groups **Figure 4**.

5. Discussion

Currently, the use of opioids is a fundamental therapy for the relief of moderate to severe pain, not only related to cancer, but also in the management of acute and chronic non-malignant pain, second only to non-steroidal anti-inflammatory drugs in terms of frequency of prescription, general for pain [22].

However, in addition to common concerns around opioid use, such as the potential for harmful side effects, physical dependence, and addiction, recent research suggests that opioids may cause opioid-induced hyperalgesia (OIH), where relief patients receiving opioids for Pain may paradoxically become more sensitive to pain as a direct result of this therapy, that is, the use of opioids can be a double-edged sword, initially providing an analgesic effect and later, they are associated with the expression of hyperalgesia reflecting the increase of compensatory regulation of pro-nociceptive pathways [23].

In this study, we observed analgesia induced by fentanyl, ketoprofen, ketamine and lidocaine in the 2nd hour after the procedures, represented by lower sensitivity to von Frey filaments compared to the group that received saline and propofol, evidencing the acute analgesic effect of the drugs. In relation to propofol, this effect, without statistical difference compared to the group that received saline solution, can be explained by the short action time of this drug administered as a bolus. On the other hand, on the 1st and 3rd days after the procedures, we found hyperalgesia with the use of fentanyl compared to the control group and the groups treated with ketoprofen, ketamine and intraperitoneally or incisional lidocaine.

In line with our results, several studies have found preemptive analgesia with the use of ketoprofen, suggesting not that COX inhibition may help only in postoperative analgesia, but also in the reduction of OIH [12] [13] [14] [15] [16] [24].

According to this scenario, laboratory investigations have reported that ketamine, the NMDA antagonists is particularly effective in reducing persistent pain associated with central sensitization in various experimental models [8] [19] [25] [26] [27] [28].

Lidocaine, a local anesthetic from the amide group, has been shown effectiveness, when administered by different routes, to be effective in the management of pain and, in our study, it was no different, since both intraperitoneally and incisional wound site showed in reducing OIH [17] [20] [29].

This effect observed with ketoprofen, ketamine and lidocaine was not observed with the use of propofol in bolus, with pain response without statistical difference to the group treated with fentanyl, differing from other studies that

used propofol in continuous infusion. This difference may have occurred due to the use of propofol bolus, unlike studies that used it in continuous infusion [30]. On the 5th day after the procedures, as observed in another study, we did not observe statistically significant differences between the groups, showing no residual hyperalgesia induced by a single dose of fentanyl [11]. Our results suggest the involvement of multiple factors in the development of OIH, including cyclooxygenases, NMDA receptors and fast sodium channels.

Hyperalgesia assessments in this study were limited to five days because another similar study showed no effects after this period [31].

6. Conclusion

The present study suggests fentanyl-induced hyperalgesia and a possible attenuating effect of this noxious effect, mediated by ketoprofen, ketamine, lidocaine, but not by bolus propofol. However, other studies should confirm these findings.

Conflicts of Interest

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

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