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Research Paper

Involvement of inflammation in severe post-operative pain demonstrated by pre-surgical and post-surgical treatment with piroxicam and ketorolac

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Keywords
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Abstract

Objectives Post-operative pain is considered to involve inflammation caused by tissue injury. However, the mechanism and timing of the involvement of inflammation in the post-operative pain remain complicated because they can vary among different types of surgery. In this study a rat incision model was used to investigate how inflammation induced by cyclooxygenases (COXs) is involved in severe post-operative pain.

Methods Longitudinal incision with a length of 1 cm was made through skin and fascia on the right hind paw of rats, starting 0.5 cm from the edge of the heel and extending towards the toes. Allodynia was evaluated using the von Frey hair test and its degree was recorded as the paw withdrawal threshold (PWT). Two non-steroidal anti-inflammatory drugs (NSAIDs), piroxicam and ketorolac, were given to rats after or before surgery, and the effects of the drugs on allodynia induced by the hind paw incision were examined.

Key findings The PWT reduction reached a sub-maximal level at 3 h, a maximal level at one day after the surgery and lasted for more than 8 days, with the parallel development of inflammation (characterized by cell infiltration and oedema). Treatment with morphine (1 mg/kg, s.c.) at one day after the surgery showed a significant anti-allodynic effect. Treatment with either piroxicam (10 mg/kg, p.o.) or ketorolac (10 mg/kg, p.o.) at one day after the surgery did not exhibit significant anti-allodynic effect, whereas pre-surgical treatment with each drug showed significant anti-allodynic effects at 3 h after surgery.

Conclusions These findings suggest the involvement of cyclooxygenases in evoking pain that occurs in the immediate post-operative period, and that an initial suppression of rapid inflammation by treatment with NSAIDs before major surgery plays an important role in the management of severe post-operative pain.

Introduction

The severity of post-operative pain is known to be primarily determined by the type of surgery.[1] It is considered that inflammatory pain accounts for a certain degree of post-operative pain and the degree of the involvement of inflammation depends on the type of surgery. After minor surgery (e.g. dental surgery), the involvement of inflammation in pain could be great because non-steroidal anti-inflammatory drugs (NSAIDs) show analgesic effects on pain after minor surgery.[2] On the contrary, although the involvement of inflammation in severe pain after major surgery may be important, treatment with NSAIDs alone cannot reduce severe post-operative pain and strong opioids such as morphine are generally used.[3,4] Thus, the involvement of the inflammation reaction in severe post-operative pain after major surgery remains unclear although inflammatory reactions, such as infiltration of leucocytes, occurs after major surgery.[5]

A rat model for post-operative pain has been developed by Brennan *et al.*[6] The model uses a plantar incision in the hind paw and is characterized by persistently reduced withdrawal thresholds to mechanical stimuli (i.e. allodynia). The degree of allodynia is greatest immediately after recovery from anaesthesia for the surgery, and the enhanced responsiveness remains notable for several days before gradually decreasing.

Many studies consistently demonstrated that morphine significantly recovered allodynia after the paw incision;[7,8] however, the efficacy of anti-inflammatory drugs in this model remains obscure. Yamamoto *et al*. showed that indometacin, an NSAID, reversed the allodynia at an oral dose of 30 mg/kg.[9] However, this dose is thought to be higher than usual, because indometacin exhibits maximal effect at a dose of 1–3 mg/kg in other classical inflammatory models.[10,11] Whiteside also showed the analgesic effect of indometacin and the cyclooxygenase (COX)-2 selective inhibitors, celecoxib and etoricoxib.[8] Kroin *et al*. reported that L-734337, a COX-2 selective inhibitor, had no effect in the rat incision model even at a sufficient dose.[12] Thus, there is no consistent opinion concerning the therapeutic effect of anti-inflammatory drugs in the rat incision model.

The relationship between the timing of treatment with NSAIDs and development of inflammation and pain has not been clarified in experimental animal models of severe post-operative pain. In this study, the relationship was clarified by evaluating the time course of histological changes and the analgesic effects of two representative NSAIDs, piroxicam and ketorolac, in a rat paw incision model. How inflammation induced by COXs is involved in severe post-operative is also described.

Materials and Methods

Chemicals

Morphine hydrochloride salt was supplied by Shionogi (Osaka, Japan). Piroxicam was synthesized by Pfizer Global Research and Development (Aichi, Japan). Ketorolac was purchased from Sigma (St Louis, USA). Oxytetracycline ointment was supplied by Pfizer Pharmaceutical Inc. (Tokyo, Japan). Methylcellulose (MC) was purchased from Wako Chemical (Osaka, Japan).

Animals

Male 7-week-old Sprague–Dawley (SD) rats were supplied by Charles River (Hino, Japan). Rats were housed in plastic cages with free access to food and water and kept under conditions of constant temperature (23 ± 2°C) and humidity (55 ± 15%) with a 12-h light–dark cycle (lights on 0700 h). The rats were housed under these conditions for 4–5 days before starting the experiment. All experimental procedures and protocols used in this study were reviewed and approved by the Animal Ethics Committee at Pfizer Inc.'s PGRD Nagoya Laboratories.

Paw incision surgery

The surgery was based on the procedure described by Brennan *et al*.[6] Following baseline evaluation, rats were placed in an anaesthetic chamber and anaesthetized with a 3–4% isofluorane O_2 mixture. The plantar surface of the right hind paw was treated with a 10% povidone-iodine solution, and a 1 cm longitudinal incision was made with a number 11 blade (Natsume, Tokyo, Japan) through skin and fascia starting 0.5 cm from the edge of the heel and extending towards the toes. The plantaris muscle was elevated using forceps and incised longitudinally. The muscle origin and insertion remained intact. After haemostasis with gentle pressure, the skin was apposed with two sutures of 5-0 nylon (Natsume, Tokyo, Japan). The wound site was covered with oxytetracycline ointment. After the surgery, the rats were allowed to recover in their cages. In the time course study, the sutures were removed under isofluorane anaesthesia two days after the surgery. In animal studies, naïve rats were anaesthetized with isofluorane but not incised.

Tactile allodynia test

The rats were habituated in grid-bottom cages before allodynia evaluation. Allodynia was evaluated by application of von Frey hair (VFH) (Semmes-Weinstein monofilaments; North Coast Medial Inc., San Jose, USA) in ascending order of force (0.008, 0.02, 0.04, 0.07, 0.16, 0.4, 0.6, 1, 1.4, 2, 4, 6, 8, 10, 15 and 26 g) to the proximal end of the wound near the lateral heel or the distal end of the wound near the palm. In the naïve rats, VFH was applied to the same area on the non-injured foot. Each VFH was applied to the paw for 6 s or until a withdrawal response occurred. Once a withdrawal response happened, the paw was re-tested with the next descending VFH until no response occurred. A force of 26 g lifted the paw, so this force was used as a cut-off point. The lowest amount of force required to elicit a response was recorded as the paw withdraw threshold (PWT).

Drug treatment

VFH tests were performed just before incision surgery and drug administration, and at indicated times after surgery or drug administration. Incised rats with a PWT below 2 g in the VFH test just before drug administration were used for the following drug assessments. The drug or vehicle was given to the rats 1 h before incision surgery, or 3 h or one day after the surgery. Morphine was dissolved in saline and injected subcutaneously in a volume of 5 ml/kg (dose, 0.3, 1 and 3 mg/kg). Piroxicam or ketorolac was suspended in 0.1% MC water solution and orally administered in a volume of 1, 3 and 10 ml/kg (dose, 1, 3 and 10 mg/kg). In all cases, the experimenter was blind to the experimental situation of each rat.

Histological study

Three hours, 1, 2, 4, 7 and 14 days after the surgery ($n = 3$ rats per group), rats were sacrificed and the whole right paws that

had been operated on were fixed immediately with 10% formalin, decalcified and embedded in paraffin. Cross sections between the two sutures were prepared and stained with hematoxylin-eosin. The paws of naïve rats were used as control.

Data analysis

The data were plotted graphically as the median force (g) of PWTs with 1st and 3rd quartiles. The difference between the vehicle group and drug groups in incised rats was analysed by the Mann–Whitney *U*-test when comparing two groups and by the Kruskal–Wallis test, followed by post-hoc Dunn's test, when comparing more than three groups. The difference between the vehicle groups in naïve rats and incised rats was analysed with the Mann–Whitney *U*-test to confirm the significant allodynic condition. $P < 0.05$ was regarded as significant.

Results

Time course of paw withdrawal threshold and histological changes after incision surgery of rat paw

The time course of PWT after plantar incision is shown in Figure 1a. Before tissue injury, median PWT was 6.0 g at the proximal end of the wound near the lateral heel. PWT was significantly reduced three hours to eight days post surgery. The minimum PWT was observed one day after incision. PWT returned to an insignificant value 16 days after the surgery. Histological analysis of incised rat paws at a various times after incision surgery was performed (Figure 1b). Inflammatory infiltration (e.g. neutrophils characterized by stained multinuclear) was already observed 3 h after surgery. The leucocytes existed on the plantar side of the dermis, hypodermis and plantaris muscles near the wound, but not on the instep side. The degree of infiltration was maximal three hours to two days after surgery, and this peak was followed by a rapid decrease. Oedema, characterized by expansion of the dermis, was observed in a parallel time course to the infiltration. By seven days after surgery the inflammation had largely been reduced. Moreover, the wound started healing just after surgery and repair of the epidermal basal layer was completed four to seven days after surgery. The plantar surface and epidermis were regenerated completely at 14 days. The same histological changes were observed in three separate rats.

Effect of post-operatively administered morphine, piroxicam and ketorolac on incision-induced allodynia

The analgesic effect of morphine, piroxicam and ketorolac on the allodynia in incised rats was evaluated one day after the incision when the minimum PWT was observed (Figure 1a). Subcutaneously injected morphine exhibited a dose-dependent analgesic effect (Figure 2a). Morphine significantly recovered PWT at the heel site 1 h after subcutaneous injection of 1 mg/kg and completely recovered PWT 0.5 and 1 h after the injection of 3 mg/kg. On the other hand, neither piroxicam (Figure 2b) nor ketorolac (Figure 2c) recovered PWT 1 h or 2 h after oral administration of 10 mg/kg, at which dose each drug is known to show beneficial effects in various inflammatory models.[10,13]

Effect of post-operatively administered piroxicam on incision-induced allodynia at different paw sites

Figure 3a shows the incision-induced PWT reduction in different paw sites one day post surgery. The pre-surgical median PWTs near the lateral heel site and at the palm site were 8.0 and 6.0 g, respectively, and there was no significant difference between them. At both sites the significant reduction in PWT was observed one day after surgery. However, the median PWT (1.0 g) at the palm site was significantly higher than that (0.40 g) near the heel site one day after surgery (Mann–Whitney *U*-test). The effect of piroxicam on allodynia induced at the palm site one day after the incision surgery was evaluated in addition to that at the lateral heel site (Figure 3b). Piroxicam did not exhibit significant analgesic effects at the palm site or at the lateral heel site 1 and 2 h after oral administration of 10 mg/kg. Under the same conditions, 3 mg/kg of morphine completely reversed PWT (data not shown).

Effect of pre-operatively administered piroxicam and ketorolac on incision-induced allodynia

As mentioned above, neither piroxicam nor ketorolac showed any analgesic effect when administered at 10 mg/kg p.o. one day after the incision surgery. Here the effects of pre-operative administration of piroxicam and ketorolac on incision-induced allodynia were investigated. Although piroxicam (10 mg/kg, p.o.) given 3 h post surgery did not recover the allodynia at the heel site 1 and 2 h after oral administration (Figure 4a), the drug given orally 1 h before the surgery inhibited allodynia at the heel site 3 h post surgery in a dose-dependent manner and significantly at 10 mg/kg (Figure 4b). However, pre-operatively administered piroxicam showed insignificant analgesic effects one day and two days after pre-operative administration. Pre-operative treatment with ketorolac also exhibited anti-allodynia effects 3 h post surgery in a dose-dependent manner and significantly at oral doses of 3 and 10 mg/kg (Figure 4c).

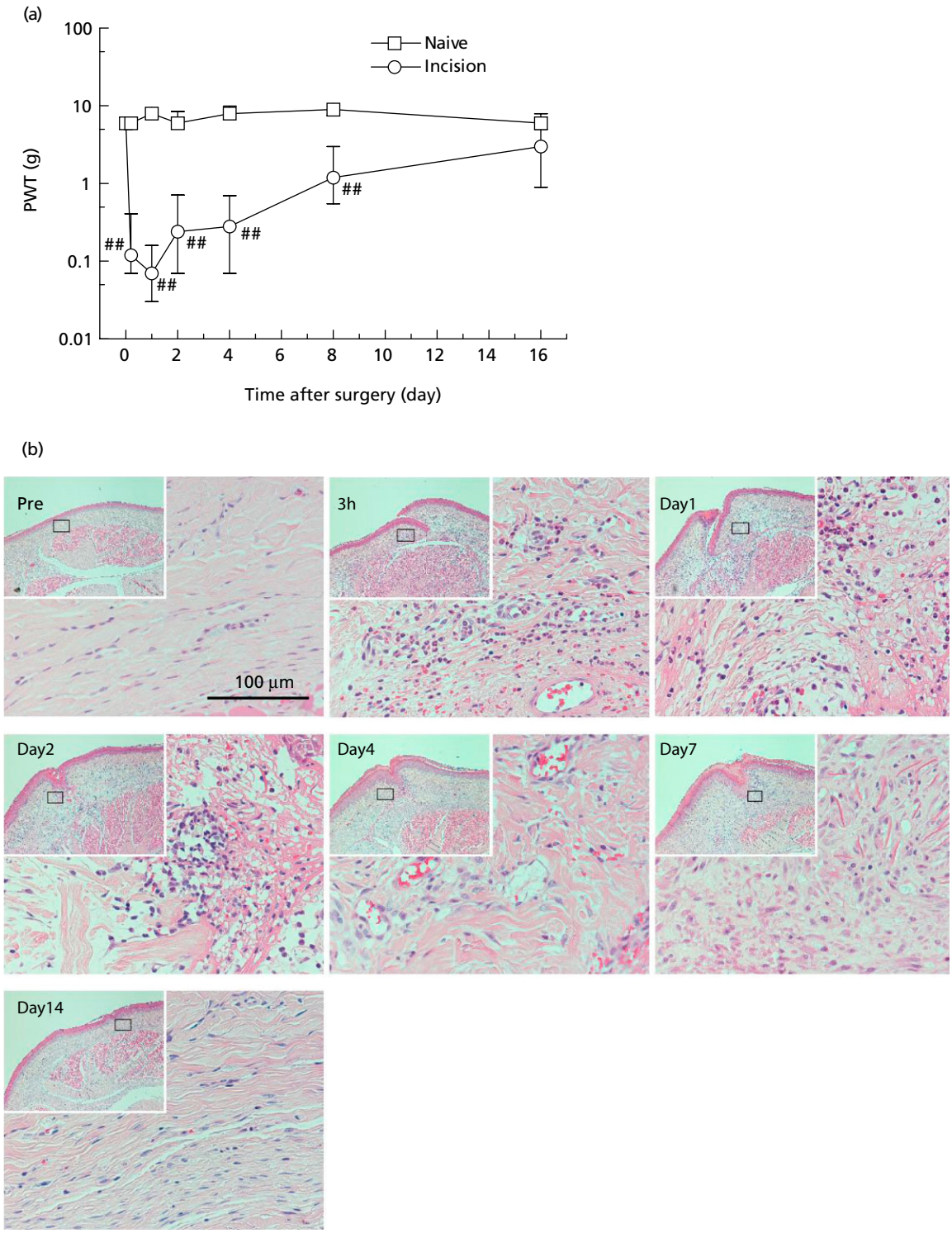

Figure 1 Time course of paw withdrawal threshold (PWT) at the heel site in the rat paw incision model and histological changes after the plantar incision. (a) PWT was measured throughout the 16 days post surgery. PWTs are expressed as medians (symbols) with 1st and 3rd quartiles (lower and upper vertical lines, respectively) for 8 rats. ##$P < 0.01$, incision group compared with the naïve group (Mann–Whitney *U*-test). (b) Typical cross-sections in the middle of sutures stained with hematoxylin-eosin in the part of the dermis (× 400) at the indicated time after the plantar incision. The small images in the left shoulder of each photograph indicate the position of the visual fields using open squire on the 10 times-down scale images, respectively. The length of the bar is 100 μm.

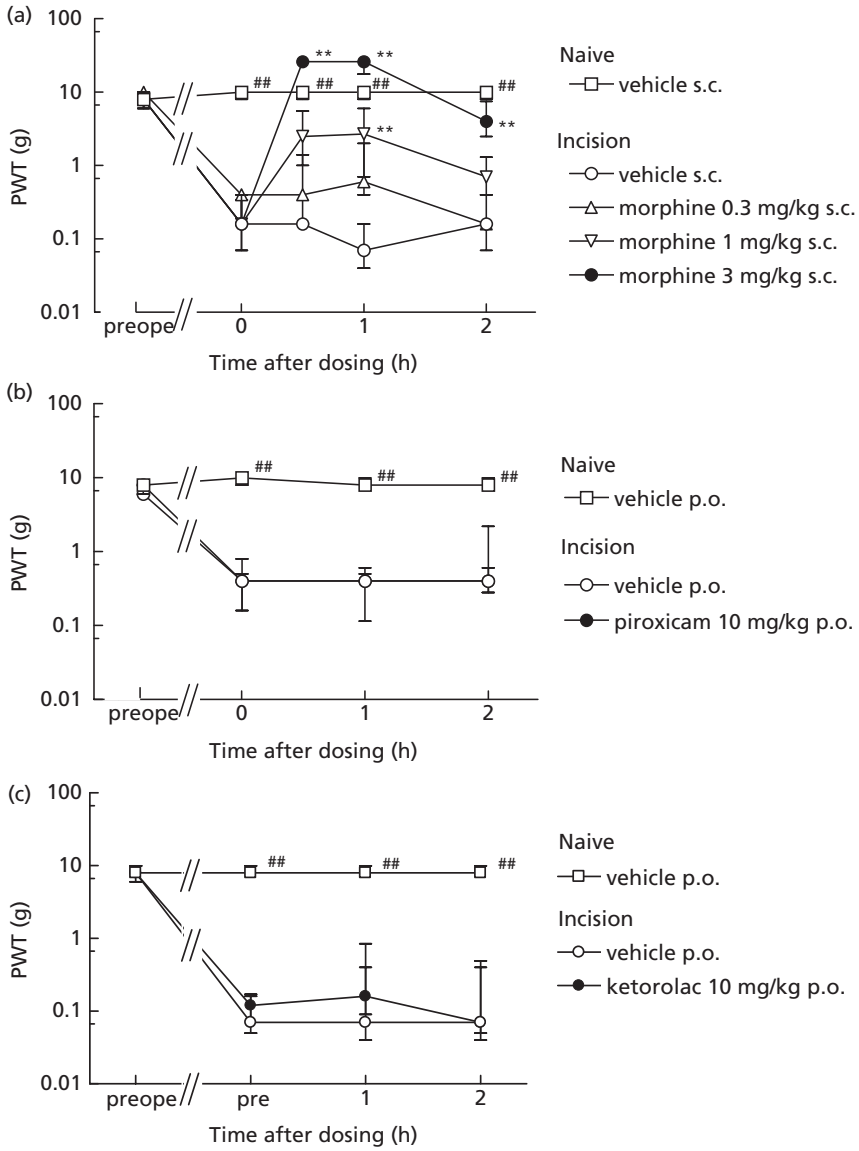

Figure 2 Effect of postoperatively administered (a) morphine, (b) piroxicam and (c) ketorolac on incision-induced allodynia one day after the plantar incision in the rat paw incision model. Morphine was administered subcutaneously and piroxicam and ketorolac were given orally, one day after the surgery. Paw withdrawal thresholds (PWTs) at the heel site were measured with von Frey hair at the times indicated. PWTs are expressed as medians (symbols) with 1st and 3rd quartiles (lower and upper vertical lines, respectively) for 8–9 rats. ##$P < 0.01$, vehicle group in incised rats compared with naïve rats (Mann–Whitney *U*-test); **$P < 0.01$, drug-administered group compared with vehicle-treated group in incised rats (Kruskal–Wallis test followed by post-hoc Dunn's test).

Discussion

In this study, we measured PWT, obtained by VFH at an area adjacent to the wound in rats with paw incision, as an indicator of post-operative pain. It was shown that a rat paw incision model demonstrated reproducible and quantifiable mechanical allodynia that lasted for several days after the incision. The time course of the hypersensitivity measured by VFH was in accordance with not only that in Brennan *et al*.'s report[6] but also the period of mechanical sensitivity observed in post-operative patients.[14,15] Moiniche *et al*. reported a very interesting clinical trial in which patients undergoing hysterectomy assessed pressure-induced pain at the place adjacent to the surgical incision as well as spontaneous pain at rest and during movement.[14] Decreases in the pressure pain threshold lasted up to 96 h after surgery in parallel with the spontaneous pain. Therefore, pressure pain threshold is one of the most important clinical indicators of

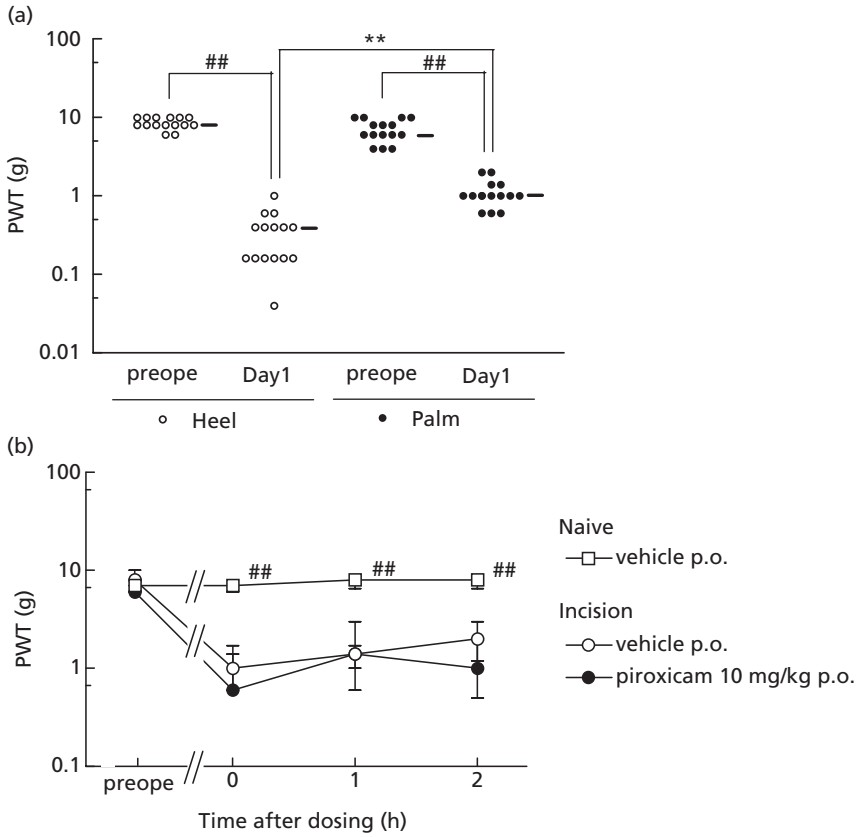

Figure 3 (a) Paw withdrawal thresholds (PWTs) in the rat paw incision model at two different sites in the same groups of rats before and one day after the plantar incision. Open circles show PWTs obtained at the heel, a site near the wound, before and after the surgery. Closed circles show PWTs obtained at the palm, a site remote from the wound, before and one day after the surgery. Bold lines show median PWTs for 14–15 rats. ##$P < 0.01$, pre-surgery compared with post surgery (Mann–Whitney *U*-test); **$P < 0.01$, PWTs at the heel compared with PWTs at the palm one day after the surgery. (b) The effects of piroxicam on incision-induced allodynia at the palm site. Piroxicam was administered orally one day after the plantar incision and PWTs at the palm site were measured with von Frey hair at the times indicated. PWTs are expressed as medians (symbols) with 1st and 3rd quartiles (lower and upper vertical lines, respectively) for 6–7 rats. ##$P < 0.01$, vehicle group in naïve rats compared with incised rats (Mann–Whitney *U*-test).

post-operative pain and the assay endpoint (i.e. PWT obtained by VFH in our rat incision model) would reflect one of the clinical endpoints in post-operative pain. Furthermore, morphine exhibited a significant anti-allodynic effect in our rat incision model. Pure opioids, in particular morphine, are the mainstay for clinical management of post-operative pain,[16] and the analgesic effects of morphine in this study also prove the validity of the evaluation using the rat incision model.

NSAIDs, such as piroxicam and ketorolac, are frequently used for the treatment of post-operative pain, but they are usually only considered suitable for treating mild-to-moderate pain.[3,4] Therefore, evaluation of NSAIDs in the rat incision model would be expected to provide information not only regarding the involvement of inflammation in post-operative pain but also the pain severity of this model. In fact, we achieved the two findings by evaluating the efficacy of two different NSAIDs, piroxicam and ketorolac, in pre-surgical and post-surgical treatment in the model.

The first finding was that piroxicam and ketorolac were not efficacious in post-surgical dosing in this study. Several reports have shown the therapeutic analgesic effects of indometacin (30 mg/kg, p.o.), a typical NSAID, against post-operative pain in the rat incision model.[8,9] The dose of indometacin tested in these studies was higher than the doses (1–3 mg/kg, p.o.) that exhibited maximal effects in other inflammatory models.[10,11] Therefore, the analgesic effects of indometacin against post-operative pain in the rat incision model may be due to a different mechanism than COX inhibition. In our study, three hours and one day post-surgical dosing with piroxicam (10 mg/kg p.o.) did not exhibit analgesic effects. Neither did ketorolac (10 mg/kg, p.o.) exhibit anti-allodynic activity in this protocol. The non-efficacy of piroxicam and ketorolac in the model would not be due to

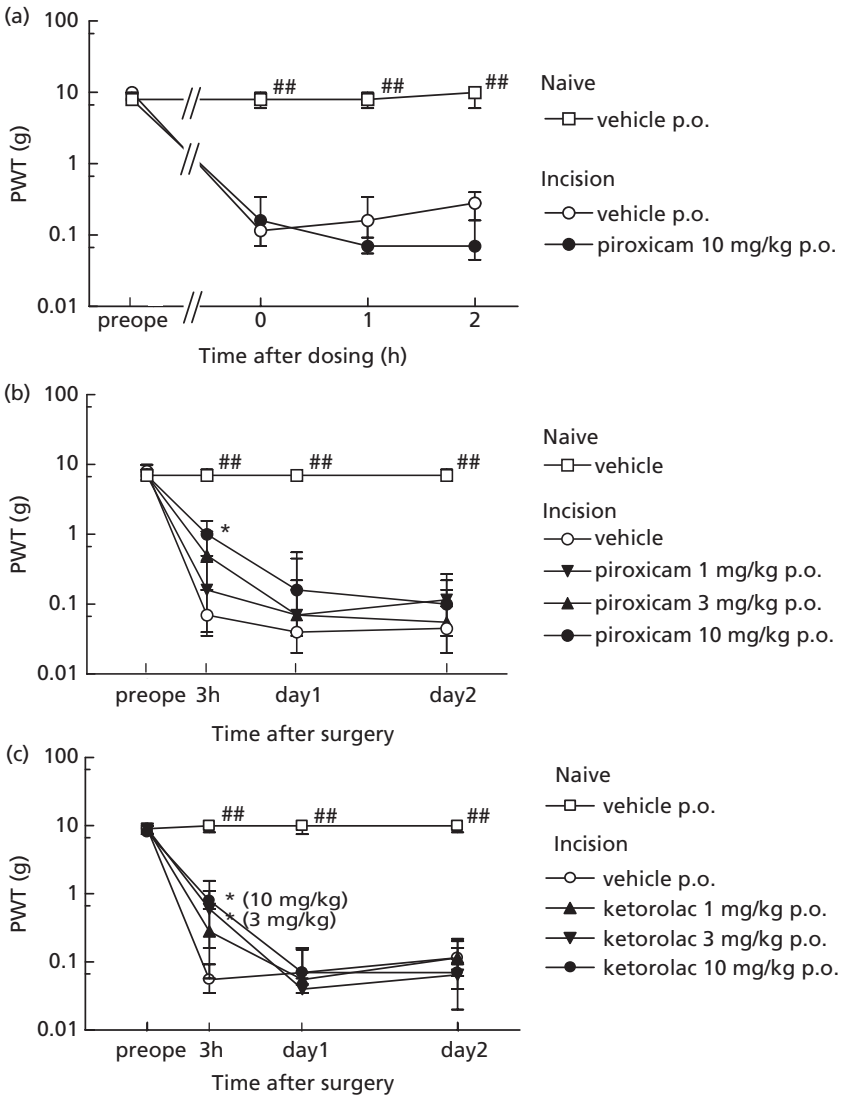

Figure 4 The effects of pre-operatively administered piroxicam and ketorolac on incision-induced allodynia in rats. Piroxicam was orally administered (a) 3 h after and (b) 1 h before the surgery. Ketorolac was orally administered (c) 1 h before the surgery. Paw withdrawal thresholds (PWTs) at the heel site were measured with von Frey hair at the indicated times post surgery. PWTs are expressed as medians (symbols) with 1st and 3rd quartiles (lower and upper vertical lines, respectively) for 7–8 rats. ##$P < 0.01$, vehicle group in naïve rats compared with incised rats at (Mann–Whitney *U*-test). *$P < 0.05$, vehicle-treated group compared with drug-administered groups in incision rats (Kruskal–Wallis test followed by post-hoc Dunn's test).

insufficient exposure, because they exhibited the maximum analgesic effects at a dose of 10 mg/kg or less in other rat inflammatory pain models, such as the carrageenan or FCA-induced mechanical hyperalgesia model.[10,13] Additionally, the non-efficacy of piroxicam is independent of the VFH application site because piroxicam did not show any analgesic effect at areas near and far from the incision site in this study. Thus, the present results of post-operative pain treatment with either piroxicam or ketorolac in the rat incision model corresponded well with those of post-operative pain treatment with NSAIDs in clinical severe post-operative pain,[3,4] and allodynia induced in the present rat incision model might reflect severe clinical post-operative pain.

The second finding of this study was that piroxicam and ketorolac were efficacious in pre-operative dosing. Either piroxicam or ketorolac given orally 1 h before surgery inhibited allodynia at 3 h after surgery. The peak time (T_{max}) and half-life ($t^1/_2$) of plasma concentration in rats to which each drug had been orally administered were 1 h and 5.2 h after piroxicam treatment (10 mg/kg, p.o.), and 20 min and 6 h after ketorolac treatment (5.6 mg/kg, p.o.), respectively.[17,18] The pharmacokinetic data well explain the anti-allodynic

effect of pre-operative treatment with piroxicam or ketorolac. Pre-operative dosing with neither piroxicam nor ketorolac inhibited allodynia at 24 and 48 h after surgery. This disappearance of efficacy after 24 and 48 h would be due to elimination of drugs from the rat blood. From these results, it would be anticipated that pre-operative treatment with NSAIDs is useful for severe post-operative pain control. Several clinical reports demonstrated the significant analgesic effect of pre-operative treatment with NSAIDs. O'Hanlon reported that early administration of tenoxicam 30 min before induction of anaesthesia prevented post-operative analgesia for 240 min in patients undergoing ambulatory breast biopsy.[19] It was also reported that piroxicam or lornoxicam administered 2 h before laparoscopic gynaecological surgery or major abdominal surgery reduced the pain score of patients.[20,21] Thus, our results in this study well reflect existing clinical reports regarding the analgesic effects of pre-operative treatment with NSAIDs after major surgery.

Pathological observation of inflammation status near the incision site is important for investigating the involvement of inflammation in post-operative pain. Inflammatory cell infiltration and oedema was already induced 3 h after the incision surgery and was observed by seven days after the surgery. Additionally, the transition of inflammatory cell infiltration and oedema after the paw incision paralleled the progression of allodynia. Thus, post-operative pain could be attributed to the cause of inflammation that occurs after the surgery. It was reported that prostaglandin E2 (PGE2) was generated by COX activation in the incision site tissue in rat thoracic muscle incision model,[22] and that PGE2, which increased in rat inflammation model, induced hyperalgesia and oedema and ketorolac suppressed them.[23] In our study suppression of oedema by pre-operative dosing with piroxicam or ketorolac was observed in rats in which the suppression of allodynia was evaluated (data not shown). The reasons why piroxicam and ketorolac showed different analgesic effects between post-operative dosing and pre-operative dosing may be due to the time-dependent transition of inflammation status after the incision. In the early stage of the inflammatory process in post-operative pain, the involvement of COXs would be essential. On the other hand, in the maintenance stage of inflammation 3 h post surgery the involvement of COXs in post-operative pain would be very small.

Conclusions

In the rat paw incision model, the transition of allodynia and inflammation proceeded in parallel after the paw incision, and two representative NSAIDs, piroxicam and ketorolac, showed anti-allodynic effects only in pre-surgical treatment. Thus, suppression of inflammation with the involvement of COXs in the early stage after the incision surgery plays an important role in suppression of the allodynia caused in parallel with inflammation. These findings suggest that treatment with NSAIDs before major surgery would be critical to clinically manage severe post-operative pain.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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