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ORIGINAL ARTICLE

Acetaminophen and non-steroidal anti-inflammatory drugs interact with morphine and tramadol analgesia for the treatment of neuropathic pain in rats

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Abstract
Purpose Although non-steroidal anti-inflammatory drugs and acetaminophen have no proven efficacy against neuropathic pain, they are frequently prescribed for neuropathic pain patients. We examined whether the combination of opioids (tramadol and morphine) with indomethacin or acetaminophen produce favorable effects on neuropathic pain and compared the efficacy for neuropathic pain with that for inflammatory pain.
Methods The carrageenan model was used as the inflammatory pain model while the tibial neuroma transposition (TNT) model was used as the neuropathic pain model. The tibial nerve is transected in the TNT model, with the tibial nerve stump then transpositioned to the lateral aspect of the hindlimb. Neuropathic pain (mechanical allodynia and neuroma pain) is observed after TNT injury. Drugs were administered orally.
Results In the carrageenan model, all drugs produced anti-allodynic effects and all drug combinations, but not tramadol + indomethacin combination, produced synergistic anti-allodynic effects. In the TNT model, tramadol and morphine, but not acetaminophen and indomethacin, produced anti-neuropathic pain effects. In the combination, with the exception of morphine + acetaminophen combination, both acetaminophen and indomethacin reduced the 50 % effective dose (ED_{50}) of tramadol and morphine as compared with the ED_{50}s for the single drug study in the TNT model. The ED_{50}s of tramadol and morphine in the carrageenan combination test were not statistically significantly different from the ED_{50}s in the TNT model combination study.
Conclusions The combination of opioids with indomethacin or acetaminophen produced a synergistic analgesic effect both in inflammatory and neuropathic pain with some exceptions. The efficacy of these combinations for neuropathic pain was not different from that for inflammatory pain.

Keywords Neuropathic pain · Inflammatory pain · Opioids · NSAIDs

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Introduction

Pain is a very complicated sensation and that involves many mechanisms of nociceptive transmission and modulation. For example, the inflammatory pain elicited by many chemical mediators, such as bradykinin, serotonin, histamine, and prostaglandin, can be effectively treated by non-steroidal anti-inflammatory drugs (NSAIDs). Neuropathic pain is refractory to NSAIDs and the first-line recommended systemic drugs are the α2δ subunit inhibitors and antidepressants, while the second-line drugs include tramadol and opioids. Thus, it is difficult to treat both inflammatory pain and neuropathic pain using a one-drug therapy [1]. Back pain is one of the most frequent complaints in pain patients. It has been reported that 35.7 % of the back pain that patients suffer from is pure neuropathic pain, while 36.3 % suffer from pure inflammatory pain, and 28.1 % have both neuropathic and inflammatory components [2]. This demonstrates that more than 50 % of back pain patients cannot be completely treated by NSAIDs alone.

Tramadol/acetaminophen fixed-dose combination capsules were recently introduced as a pain medication and

have been shown to be effective against many pain conditions, such as osteoarthritis and low back pain [3]. While NSAIDs and acetaminophen have no proven efficacy against neuropathic pain, they are frequently prescribed for neuropathic pain patients [4]. Thus, it is important to verify whether the combination of an opioid with NSAIDs or acetaminophen is effective against neuropathic pain.

Recently, Dorsi et al. [5] described a new rat neuropathic pain model, which they called the tibial neuroma transposition (TNT) model. In this model, the posterior tibial nerve is cut, with the cut nerve end then transpositioned to the lateral aspect of the hindlimb. Neuroma develops at the nerve stump, and mechanical stimulation of the neuroma will produce withdrawal behavior (neuroma pain). Mechanical allodynia also develops at the plantar surface of the hind paw. Neuroma pain is the typical pain that is seen following complete nerve injury while mechanical allodynia is usually observed after an incomplete nerve injury. Thus, there are two distinctly different neuropathic pains observed in this model.

In the present study, we first determined whether the oral administration of a combination of opioids (morphine and tramadol) with a NSAID (indomethacin) or acetaminophen would produce a synergistic analgesic effect on either the inflammatory pain (carrageenan model) or the neuropathic pain (allodynia and neuroma pain in the TNT model). Next, we then compared the efficacy of each of these combination therapies when they were used to treat neuropathic pain and inflammatory pain.

Methods

This investigation was performed under a protocol approved by the Institutional Animal Care Committee, Kumamoto University, Kumamoto, Japan. Male Sprague–Dawley rats (Japan SLC, Inc., Shizuoka, Japan) weighing 200–300 g were used.

Carrageenan model

After suspending 1 mg of lambda carrageenan (Sigma Chemical, St. Louis, MO, USA) in 0.1 ml normal saline, it was subcutaneously injected into the plantar surface of the left hind paw. Mechanical allodynia occurred at the carrageenan-injected plantar surface.

TNT model

TNT model operations were performed according to the method described by Dorsi et al. [5]. The tibial nerve was tightly ligated and transected just proximal to the plantar bifurcation. The needle-bearing end of the suture that was used to ligate the tibial nerve was passed through the subcutaneous tunnel and pushed through the skin at a location that was 8–10 mm superior to the lateral malleolus. The suture was gently pulled to advance the tibial nerve stump through the subcutaneous tunnel until it was flush with the inner surface of the skin.

One week after the operation, mechanical allodynia developed at the middle of the plantar surface where the tibial nerve was innervated while neuroma pain was observed at the transpositioned site of the tibial nerve stump.

Assessment of mechanical allodynia and neuroma pain

Mechanical thresholds were measured using von Frey filaments (Stoelting, Wood Dale, IL, USA) with logarithmically incremental stiffnesses (0.41, 0.70, 1.20, 2.00, 3.63, 5.50, 8.50, and 15.1 g). Measurements were used to calculate the 50 % probability thresholds for mechanical paw withdrawal [6, 7].

Neuroma pain was evaluated by measuring the number of paw withdrawals during ten repetitive applications of a 150-mN von Frey filament to the location of the neuroma, using an inter-stimulus interval of 1 s [8].

Drugs and administration

The agents used in this study were tramadol (Nippon Shinyaku, Kyoto, Japan), morphine hydrochloride (Takeda, Osaka, Japan), acetaminophen (Sigma, St. Louis, MO), indomethacin (Sigma), naloxone hydrochloride (Sigma), and carboxymethyl cellulose (CMC; Wako, Osaka, Japan). For the oral administrations, a stainless-steel tube was inserted through the esophagus to the stomach of the restrained animals. Tramadol and morphine were dissolved in 2 ml of saline. Acetaminophen and indomethacin were suspended in 2 ml of a 0.5 % CMC solution. A preliminary study revealed that administration of 100 mg/kg of indomethacin in normal untreated rats caused them to die within 7 days after the drug administration, while rats administered 30 mg/kg of indomethacin showed normal feeding and a normal weight gain. Thus, 30 mg/kg of indomethacin was the largest dose administered in this study. Naloxone was dissolved in saline, with a 1-ml final volume injected intraperitoneally (IP).

Experimental protocol

Single drug study

Carrageenan model

A preliminary study performed in our laboratory revealed that the maximum level of mechanical allodynia developed

about 6 h after the carrageenan injection, with this level maintained for at least 3 h. Baseline data were obtained at 6 h after the carrageenan injection. Subsequently, we then administered the test drugs to each animal and tested at 15, 30, 60, 75, 90, 105, and 120 min after the oral administration.

TNT model

A preliminary study performed in our laboratory revealed that the maximum mechanical allodynia and the maximum neuroma pain were observed between 7 and 21 days after the nerve injury. Thus, each animal received 1–3 medications administered orally at intervals of at least 3 days from 7 days after creation of the nerve lesion.

Baseline data were obtained prior to the drug administration. We then administered test drugs to each animal and measured the mechanical allodynia and neuroma pain at 15, 30, 60, 75, 90, 105, and 120 min after the oral administration.

Combination study with two drugs

For the combination study with two drugs, acetaminophen + tramadol, indomethacin + tramadol, acetaminophen + morphine, or indomethacin + morphine were coadministered.

In the carrageenan model study, the dose ratio of the two drugs for each combination was determined in accordance with the 50 % effective dose (ED_{50}) of each drug established in the single drug study (acetaminophen:tramadol = 5:1, indomethacin:tramadol = 1:2, acetaminophen:morphine = 6:1 and indomethacin:morphine = 1:2). For the TNT model study, we were unable to determine the ED_{50}s for acetaminophen and indomethacin in the single drug study. Thus, we chose the same dose ratios used in the carrageenan model. After obtaining the baseline data, the animals were tested at 15, 30, 60, 75, 90, 105 and 120 min after drug administration.

In both single drug and combination study, to determine whether the analgesic effects of tramadol and morphine were mediated by the activation of an opioid receptor, 1 mg/kg of naloxone was administered IP. Naloxone was administered when the effect of either morphine or tramadol was maximum.

Statistical analysis

Mechanical allodynia in carrageenan and TNT models

To determine whether carrageenan injection induced significant mechanical allodynia, we used the Mann–Whitney rank-sum test to compare the 50 % probability threshold before and at 6 h after the carrageenan injection. To determine whether TNT induced significant mechanical allodynia, we used the Mann–Whitney rank-sum test to compare the 50 % probability threshold before the nerve injury and just before the drug administration.

To analyze the dose-dependence, we calculated the percentage maximum possible effect (%MPE), where %MPE = ([post-drug maximum 50 % probability threshold − pre-drug 50 % probability threshold]/[15.0 g (maximum limit of 50 % probability threshold) − pre-drug 50 % probability threshold]) × 100. The post-drug maximum 50 % probability threshold was defined as the single highest 50 % probability threshold after the drug administration. To evaluate the dose dependence, we used a one-way analysis of variance (ANOVA) with a Dunnett multiple comparison test. The ED_{50} and 95 % confidence intervals (95 % CI) for the dose–response curves for the %MPEs were also calculated using computer software (CalcuSyn, Ver 2.0, Biosoft, Cambridge, UK). In the antagonist study, a paired *t* test was used.

In the combination study, dose dependence was analyzed by linear regression analysis. To determine whether the antiallodynic interaction of drugs was additive or synergistic in the carrageenan model study, we performed isobolographic analysis using CalcuSyn [9]. The synergism between two drugs was quantified by combination indexes using CalcuSyn. A combination index indicates synergism when <0.9, antagonism when >1.1 and additivity when between 0.9 and 1.1 [10]. However, we could not perform the isobolographic analysis in the TNT model study, as the ED_{50}s of indomethacin and acetaminophen could not be determined.

Neuroma pain

To analyze the effects of drugs on the response frequency, we calculated the area under the curve (AUC) of the entire time-effect curve by the trapezoidal rule. Since it was not possible to standardize the AUC data, raw data were used to analyze the drug effects. As a result, we were unable to calculate the ED_{50} in the neuroma pain study. To evaluate dose dependence, we used a one-way ANOVA with a Dunnett multiple comparison test. In the antagonist study, a paired *t* test was used, while in the combination study we used linear regression analysis to evaluate the dose dependence.

Wherever appropriate, results were expressed as the mean ± SEM. Critical values that reached a $p < 0.05$ level of significance were considered statistically significant.

Results

Carrageenan model study

The 50 % probability threshold at 6 h after carrageenan injection (pre-drug 50 % probability threshold; 0.89 ± 0.073 g

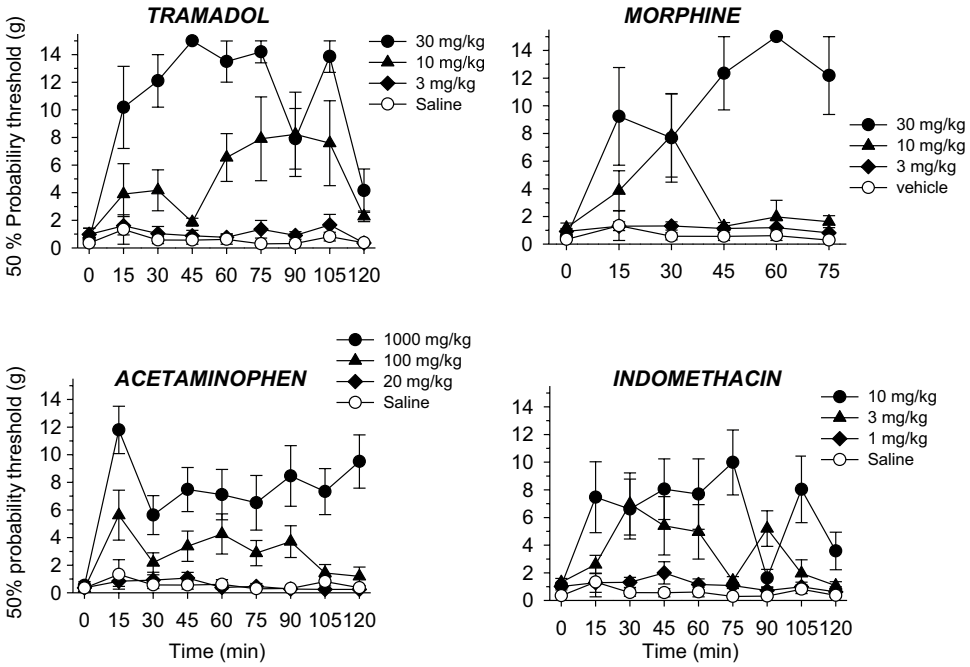

Fig. 1 Time-effect curves for orally administered tramadol, morphine, acetaminophen, and indomethacin on mechanical allodynia in the carrageenan model study. Ordinate: 50 % probability threshold (g); abscissa: time after drug administration (min). Each *line* represents the group mean and SEM of 5–9 rats

Table 1 ED50 values in carrageenan test and TNT model test

	Drug	Carrageenan test		TNT model (allodynia)	
		ED50	95 % CI	ED50	95 % CI
Single drug study	Tramadol	4.8	3.0–7.0	15.9	10.4–24.5
	Morphine	5.1	3.5–7.4	5.3	3.1–9.1
	Acetaminophen	32.8	18.8–57.2	–	
	Indomethacin	2.1	1.3–3.4	–	

		Ratio	ED50	95 % CI	Combination index	ED50	95 % CI
Two drugs combination study	Tramadol acetaminophen	1	0.9	0.7–1.3	0.4	4.6	3.1–6.9
		5	4.7	3.4–6.5		23.2	15.5–34.7
	Tramadol indomethacin	2	1.9	1.4–2.6	0.9	3.7	2.1–5.9
		1	0.9	0.7–1.3		1.9	1.2–3.0
	Morphine acetaminophen	1	1.5	1.1–2.1	0.6	1.5	0.7–3.2
		6	9.2	6.8–12.6		9.3	6.9–12.5
	Morphine indomethacin	2	1.1	0.5–2.2	0.5	1.9	1.2–2.3
		1	0.5	0.3–1.1		0.9	0.6–1.5

–, unable to calculate

($n = 147$)) was significantly less than the pre-carrageenan 50 % probability threshold (15.0 ± 0.00 g) ($p < 0.0001$). These data indicated that the carrageenan injection induced significant mechanical allodynia.

There were no statistically significant differences in the mean pre-drug 50 % probability thresholds after grouping the animals (data not shown, $p > 0.2$ by one-way ANOVA).

Effects of acetaminophen, indomethacin, tramadol, and morphine

Acetaminophen, indomethacin, tramadol and morphine attenuated the level of the allodynia in a dose-dependent manner (Fig. 1; Table 1, $p < 0.001$).

In the combination studies, acetaminophen + tramadol, acetaminophen + morphine, indomethacin + tramadol

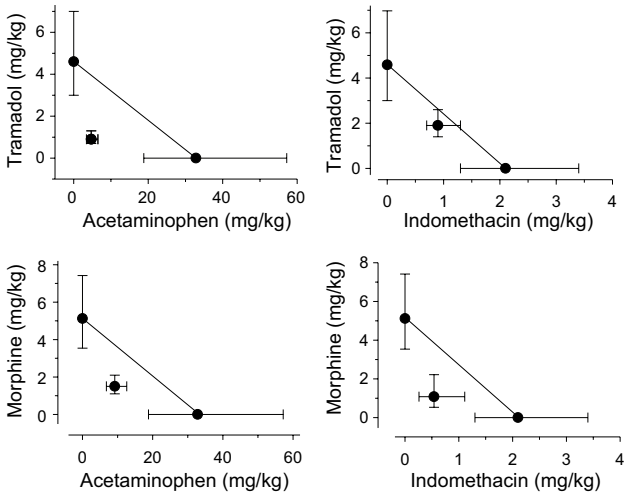

Fig. 2 Isobolograms of the combination study (acetaminophen + tramadol, indomethacin + tramadol, acetaminophen + morphine, and indomethacin + morphine) in the carrageenan study. Isobolograms demonstrated that acetaminophen + tramadol, acetaminophen + morphine, and indomethacin + morphine combinations, but not the indomethacin + tramadol combination, produced a synergistic effect on the mechanical allodynia in the carrageenan study

and indomethacin + morphine produced dose-dependent anti-allodynic effects (data not shown, $p < 0.002$). Isobolographic analysis revealed that synergistic interactions between acetaminophen and tramadol, acetaminophen and morphine, and indomethacin and morphine, but not the indomethacin and tramadol combination (combination index = 0.9), existed (Fig. 2; Table 1).

In both the single drug study and the combination study, the effect of both tramadol and morphine was completely antagonized by 1 mg/kg naloxone (Fig. 3, tramadol: $p < 0.001$; morphine: $p < 0.02$, by paired t test).

TNT model study

The 50 % probability threshold just before the drug administration (pre-drug threshold: 1.3 ± 0.057 g (n = 169)) was significantly less than the pre-surgery 50 % probability threshold (15.0 ± 0.00 g) ($p < 0.0001$). Response frequency (%) just before the drug administration (pre-drug response frequency: 49.7 ± 18.6 %, n = 181) was significantly larger than the pre-surgery response frequency (0 ± 0.00 %) ($p < 0.001$). These data indicated that TNT induced significant mechanical allodynia and neuroma pain.

There were no statistically significant differences in the mean pre-drug 50 % probability thresholds and pre-drug response frequency after grouping the animals (data not shown, $p > 0.2$ by one-way ANOVA).

Effects of acetaminophen, indomethacin, tramadol, and morphine

Tramadol and morphine attenuated the level of allodynia and decreased the AUC of the response frequency curve in a dose-dependent manner (Figs. 4, 5, $p < 0.001$). On the other hand, acetaminophen had no effect on the level of the mechanical allodynia and the AUC of the response frequency curve (Figs. 4, 5, $p > 0.2$). Indomethacin at a dose between 0.3 and 30 mg/kg significantly decreased the level of the mechanical allodynia, but had no effect on the neuroma pain (Figs. 4, 5, allodynia: $p < 0.01$; neuroma pain: $p > 0.7$). However, even at 30 mg/kg indomethacin, %MPE was 55.9 ± 14.3 % and thus, it was not possible to determine the ED_{50}.

In the combination studies, acetaminophen + tramadol, acetaminophen + morphine, indomethacin + tramadol, and indomethacin + morphine produced dose-dependent anti-allodynic and anti-neuroma pain effects (Fig. 6, anti-allodynic effect: $p < 0.005$; Fig. 7, anti-neuroma pain effect: $p < 0.05$ by linear regression analysis).

In both the single drug study and the combination studies, the effect of both tramadol and morphine were completely antagonized by 1 mg/kg naloxone (Fig. 3, tramadol: $p < 0.02$; morphine: $p < 0.005$, paired t test).

ED_{50} of anti-allodynic effect (Table 1)

In both the carrageenan and the TNT model studies, with the exception of the morphine + acetaminophen combination in the TNT model, the ED_{50}s for both tramadol and morphine in the single drug study were significantly larger than the ED_{50}s when acetaminophen and indomethacin were coadministered.

In the combination studies with two drugs, although the ED_{50}s for the tramadol + acetaminophen combination in the carrageenan test were significantly lower than those in the TNT model, the ED_{50} for the tramadol + indomethacin combination in the carrageenan test was not significantly different from the ED_{50}s in TNT model study. ED_{50}s for morphine when administered as morphine + indomethacin or morphine + acetaminophen in the carrageenan test were similar to those calculated in the TNT model.

Discussion

In the present study, oral administration of either morphine or tramadol produced a significant analgesic effect in both the carrageenan test and the TNT model study. Oral administration of either indomethacin or acetaminophen produced a significant analgesic effect in the carrageenan test, but

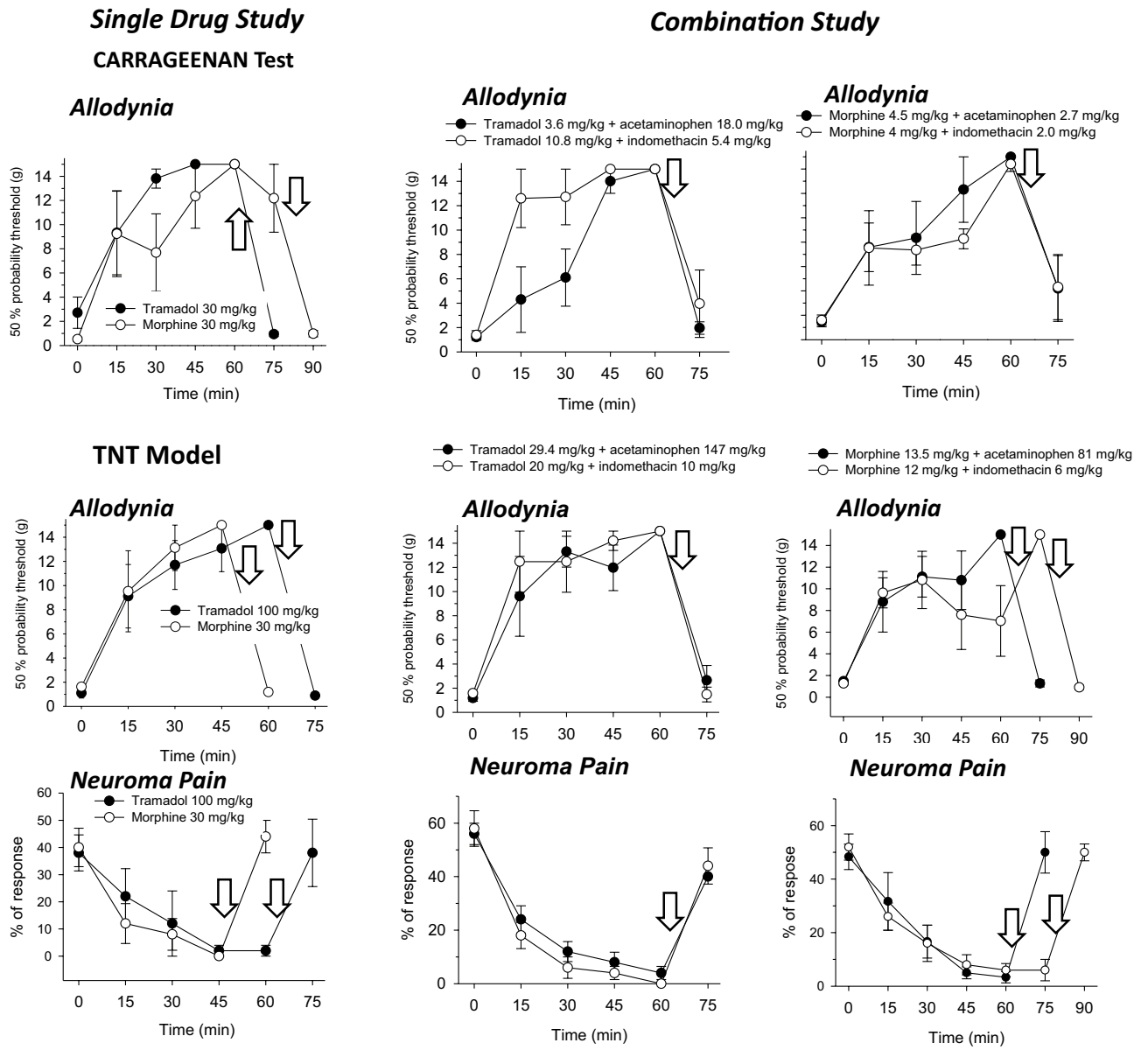

Fig. 3 IP administration of naloxone antagonized the effect of tramadol and morphine in both carrageenan study and TNT model study. Naloxone was administered when the effect of either morphine or tramaodl was maximum. The time of morphine to achieve the maximum effect was different from that of tramadol. Moreover, in the morphine combination study, the time of morphine + indomethacin to achieve the maximum effect was different from that of morphine + acetaminophen. Thus, naloxone was administered 45, 60, or 75 min after the drug administration (*up arrow* or *down arrow* indicated the time of IP naloxone). In each case, naloxone completely antagonized the analgesic effect of tramadol and morphine in both carrageenan study and TNT model study

not in the TNT model study. As previously reported, single drug therapies using either NSAID or acetaminophen had no effect on neuropathic pain [4].

In the carrageenan test, with the exception of the tramadol + indomethacin combination, the coadministration of opioid (morphine or tramadol) with indomethacin or acetaminophen produced a synergistic analgesic effect. In the TNT model study, with the exception of the morphine + acetaminophen combination, the coadministration of opioid (morphine or tramadol) with indomethacin or acetaminophen significantly reduced the ED_{50}s of both tramadol and morphine as compared to the values for the single drug study. Although both acetaminophen and indomethacin had no effect on neuropathic pain in the single drug study, these data strongly suggested that coadministration of opioid with either acetaminophen or indomethacin shifted the dose–response curves of tramadol or morphine for the TNT model study to the left. Although it was not

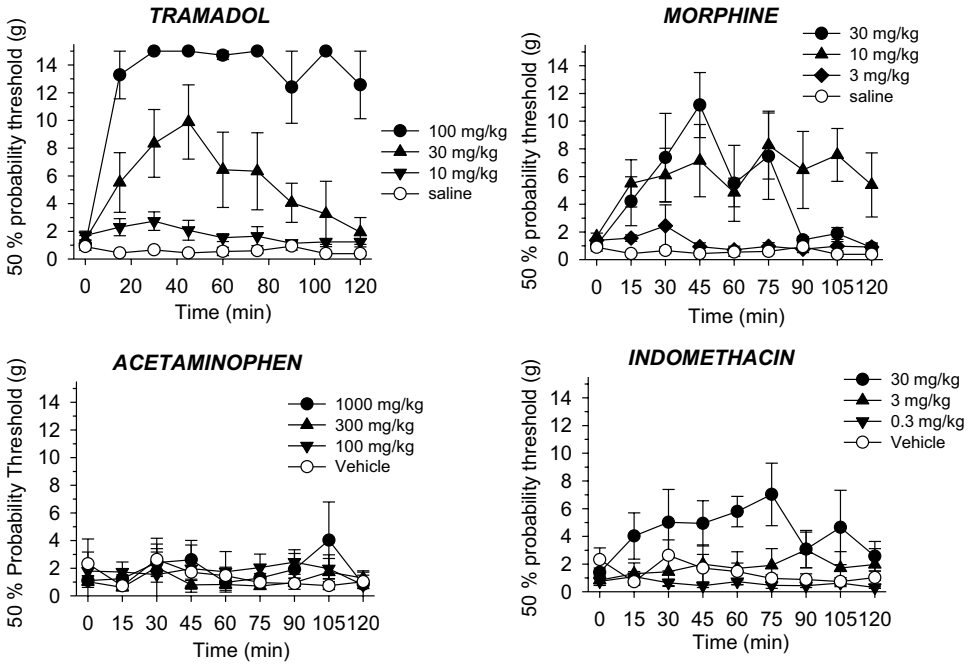

Fig. 4 Time-effect curves for orally administered tramadol, morphine, acetaminophen, and indomethacin on the mechanical allodynia in the tibial neuroma transposition (TNT) model study. Ordinate: 50 % probability threshold (g); abscissa: time after drug administration (min). Each *line* represents the group mean and SEM of 5–9 rats

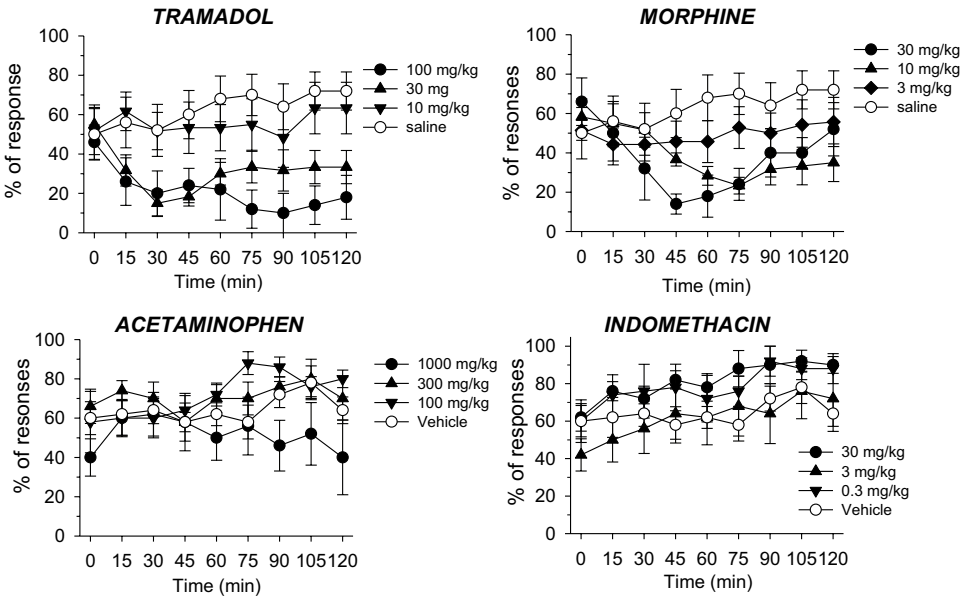

Fig. 5 Time-effect curves for orally administered tramadol, morphine, acetaminophen, and indomethacin on neuroma pain in the tibial neuroma transposition (TNT) model study. Ordinate: percentage responses to 10 applications of a von Frey filament (%); abscissa: time after drug administration (min). Each *line* represents the group mean and SEM of 5–9 rats

possible to calculate ED_{50}s of tramadol and morphine for neuroma pain in the neuroma pain study, coadministration of opioids (morphine and tramadol) with acetaminophen and indomethacin produced a dose-dependent anti-neuroma pain effect at the same dose range as the anti-allodynic effect. These data strongly suggest that coadministration of opioids with indomethacin or acetaminophen produced synergistic analgesic effects on both the inflammatory pain model and the neuropathic pain model with some exceptions. These analgesic effects were completely antagonized by IP naloxone, which suggests that the analgesic effects of either morphine or tramadol are mediated by the μ opioid receptor activation. Although tramadol was known to act as an inhibitor of noradrenalin and serotonin reuptake, the analgesic effect of tramadol presented in this study was mediated only by an μ opioid receptor activation. Contribution of the property of being a noradrenalin and serotonin reuptake inhibitor to an analgesic effect of tramadol might be relatively small in the present study.

In the combination study, the ED_{50}s of tramadol in the tramadol and acetaminophen combination group in the carrageenan test were significantly lower than the ED_{50}s calculated

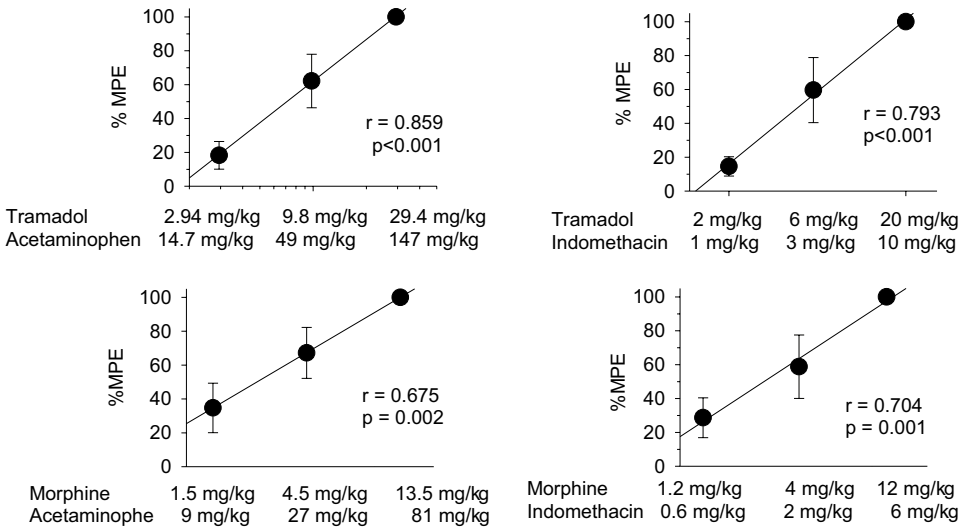

Fig. 6 Dose–response curves of the combination study (acetaminophen + tramadol, indomethacin + tramadol, acetaminophen + morphine, and indomethacin + morphine) on mechanical allodynia. In this combination study, the ratio of acetaminophen, indomethacin, tramadol and morphine was fixed (acetaminophen:tramadol = 5:1, indomethacin:tramadol = 1:2, acetaminophen:morphine = 6:1 and indomethacin:morphine = 1:2), with the ratios determined based on the ED_{50} values of each drug calculated in the carrageenan study. Dose–response curves demonstrated that all drug combinations produced an anti-allodynic effect. Each *line* represents the group mean and SEM of 5–9 rats

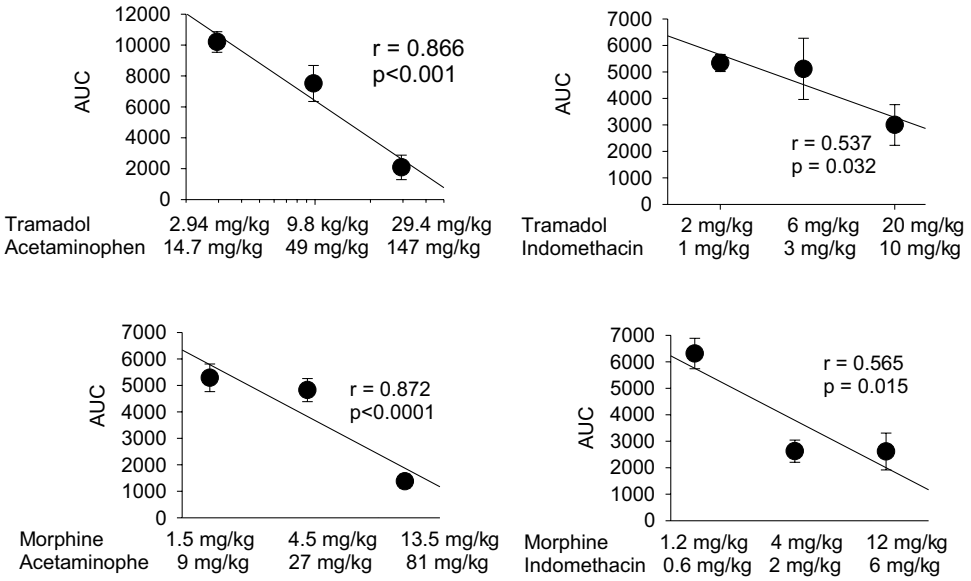

Fig. 7 Dose-response curves of the combination study (acetaminophen + tramadol, indomethacin + tramadol, acetaminophen + morphine, and indomethacin + morphine) on neuroma pain. In this combination study, the ratio of acetaminophen, indomethacin, tramadol and morphine was fixed (acetaminophen:tramadol = 5:1, indomethacin:tramadol = 1:2, acetaminophen:morphine = 6:1 and indomethacin:morphine = 1:2), with the ratios determined based on the ED_{50} values of each drug calculated in the carrageenan study. Dose-response curves demonstrated that all drug combinations produced an anti-neuroma pain effect. Each *line* represents the group mean and SEM of 5–9 rats

in the TNT model study. However, the ED_{50}s for both tramadol and morphine in the other three combination groups in the carrageenan test were not significantly different from the ED_{50}s in the TNT model. Tramadol is a weak opioid and morphine is a strong opioid. This efficacy difference may contribute to the inferiority seen for the tramadol administration.

In the present study, all drugs applied in this study were administered orally. In the clinical situation, the drug combinations examined in this study were frequently administered orally for the treatment of pain [11, 12]. Our study provided clinically relevant data.

The mechanisms of acetaminophen to act as an analgesic drug are still not fully understood. Acetaminophen is metabolized to the primary amine *p*-aminophenol in the liver and *p*-aminophenol is further conjugated in the brain and the spinal cord with arachidonic acid to form the bioactive fatty acid amide *N*-acylphenolamine (AM404) [13]. AM404 has been reported to inhibit isolated COX-1 and COX-2 as well as LPS-induced prostaglandin E2 formation in a concentration-dependent manner [13]. Moreover, AM404 is also a potent activator of TRPV1 [14, 15]. AM404 acts as an agonist of a cannabinoid CB1 receptor and an inhibitor of cellular anandamide uptake [16]. It has been speculated that acetaminophen used all these mechanisms to produce an analgesic effect. In the present study, both acetaminophen and indomethacin potentiated an analgesic effect of either tramadol or morphine with a similar manner. Indomethacin acts as a COX-1 and COX-2 inhibitor. NSAIDs decrease the production of prostaglandin E2 at the site of inflammation and produce anti-inflammatory and analgesic effects [17]. This indicated that primary target of NSAIDs to produce anti-inflammatory and analgesic effects was peripheral COX inhibition. On the other hand, NSAIDs are known to cross the blood–brain barrier. Especially, indomethacin has a good passage property of the blood–brain barrier [18]. It has been reported that systemically administered indomethacin inhibited neurogenic plasma extravasation at the dura mater induced by electrical stimulation [19]. These data strongly suggested that NSAIDs, especially indomethacin, acted at the brain. Although the precise mechanisms of indomethacin and acetaminophen to produce a synergistic effect with morphine and tramadol are unknown, these data suggested that either acetaminophen or indomethacin produced a synergistic analgesic effect with either tramadol or morphine using the property of being an inhibitor of the brain COX-1 and COX-2, but not the peripheral COX-1 and COX-2. On the other hand, the inhibition of brain COX-1 and COX-2 itself had no effect on neuropathic pain.

In our previous report, we found that an oral administration of either pregabalin or duloxetine produced anti-allodynic effects in the TNT model, but did not have any anti-neuroma pain effects [8]. Furthermore, this previous study also showed that oral coadministration of morphine with either pregabalin or duloxetine produced a synergistic anti-allodynic effect and not an anti-neuroma pain effect. In the present study, we demonstrated that opioid + (indomethacin or acetaminophen) combination produced synergistic anti-allodynic (Fig. 6) and anti-neuroma pain (Fig. 7) effects in the TNT model. These data demonstrate the superiority of the opioid (morphine or tramadol) + (indomethacin or acetaminophen) combination over the morphine + (pregabalin or duloxetine) combination, and suggest this combination may be a promising regimen for the treatment of both inflammatory and neuropathic pain.

In conclusion, although some exceptions existed, the combination of opioids with NSAIDs or acetaminophen produced synergistic analgesic effects in both inflammatory and neuropathic pain, with the efficacy of these combinations in treating inflammatory pain not significantly different from that for neuropathic pain. This combination therapy might be a new beneficial option for treating neuropathic pain.

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