Paclitaxel-associated Acute Pain Syndrome Similarly Occurs in the Patients with or without Previously Administered Non-steroidal Anti-inflammatory Drugs Prior to Paclitaxel Administration

Yoshitaka Saito, Takehiro Yamada, Masaki Kobayashi, Jun Sakakibara-Konishi, Naofumi Shinagawa, Ichiro Kinoshita, Hirotoshi Dosaka-Akita, and Ken Iseki

Departments of Pharmacy, Hokkaido University Hospital; First Department of Medicine, Hokkaido University Hospital; Medical Oncology, Hokkaido University Faculty of Medicine and Graduate School of Medicine; Laboratory of Clinical Pharmaceuticals & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University; and Department of Clinical Pharmaceutics & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University.

(Rceived May 30, 2019; Accepted August 9, 2019)

Paclitaxel (PTX)-associated acute pain syndrome (P-APS) is characterized by disabling but transient arthralgia and myalgia in up to 80% of patients administered with PTX. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely administered to patients with cancer who have pain or fever, and are mainly used to manage P-APS. In this study, we investigated how P-APS appear in the patients who were administered NSAIDs prior to PTX injection. The incidence or severity and duration of P-APS in patients previously administered NSAIDs were compared to those of patients who were not administered NSAIDs. The relationship between previously administered NSAIDs and rescue administration for the relief of P-APS was also evaluated. It was revealed that the incidence and duration of P-APS were 72% and 4.67 ± 2.30 d, respectively, in the control group and 84% and 6.19 ± 3.30 d, respectively, in the NSAIDs group. There was no significant difference in the incidence and duration and the severity of P-APS between the two groups. Patients who were previously administered NSAIDs tended to obtain less pain relief from NSAIDs administered as rescue medications, and needed other medication. Univariate and multivariate analysis revealed no correlation between previously administered NSAIDs or patient characteristics and the incidence of P-APS. In this study, it was found that clinical condition that needs NSAIDs and previously administered NSAIDs prior to PTX injection do not affect the incidence, severity, and duration of P-APS. These results will help in educating patients about their medications and will contribute to the management of P-APS.

Key words—paclitaxel; paclitaxel-associated acute pain syndrome; pain; non-steroidal anti-inflammatory drugs; arthralgia; myalgia

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, and the number of patients with lung cancer is increasing. Non-small-cell lung cancer (NSCLC) accounts for 85% of cases of lung cancer. Most of the patients with NSCLC are diagnosed in the advanced stage. Chemotherapy is the main treatment for advanced NSCLC. Carboplatin plus paclitaxel (PTX) (plus bevacizumab, in cases of non-squamous cell lung cancer) is one of the most widely used regimens for the first-line therapy against advanced NSCLC.1,2 It is important to manage the adverse effects caused by chemotherapeutic agents for the safe implementation of anti-cancer treatment and the maintenance of the quality of life of the patients.

PTX-associated acute pain syndrome (P-APS) is characterized by disabling but transient arthralgia and myalgia in up to 80% of patients who were administered PTX.3-6 These adverse events typically occur 1 to 3 d after PTX administration and resolve within a week; these often significantly affect patients’ activities of daily living for several days.3-6 Although the pathophysiology of P-APS needs further study, it has been reported that P-APS is caused by nociceptor sensitization based on the patients’ descriptions of pain. It has also been reported that rats administered PTX develop nerve injury within 24 h.7 On the other hand, it has been reported that P-APS is considered quite distinct from chemotherapy-induced peripheral neuropathy (CIPN), with different mechanisms of action and temporal profiles; the occurrence of P-APS can predispose an individual to CIPN,8 Corticosteroids,9,10 glutamine,11 Shakuyaku-Kan-
to-To (a Japanese herbal medicine),12 and gabapentin13 prevent P-APS, although there are conflicting results regarding glutamine.11,14 Non-steroidal anti-inflammatory drugs (NSAIDs) are primarily administered in order to relieve P-APS.12 However, narcotic drugs are sometimes prescribed due to the severity of symptoms. It has been suggested that age, sex, height, prior chemotherapy, renal or hepatic function, and the metastatic sites do not have a significant correlation with P-APS.5 There are some reports regarding the correlation between P-APS and a single or cumulative PTX dose5,15,16 or duration of PTX infusion.15,17 However, these results are incompatible. Thus, the relationships between dose, infusion time of PTX, and P-APS are still unclear. Furthermore, pain and/or fever often occur in patients with advanced lung cancer, and NSAIDs are mainly administered for their management. It is also unknown how P-APS manifests in patients who have already been administered NSAIDs for pain or fever prior to PTX injection. Since NSAIDs are often administered to deal with P-APS, it was hypothesized that patients administered NSAIDs prior to PTX injection could have less or milder P-APS.

Therefore, for more accurate prediction and supportive care of P-APS, it is important to determine whether patients administered NSAIDs prior to chemotherapy experience P-APS similar to patients who were not administered NSAIDs.

This study was performed to investigate whether clinical condition that needs NSAIDs and previously administered NSAIDs prior to PTX injection affect the incidence, severity, and duration of P-APS, and to understand the risk or attenuating factors for the incidence of P-APS.

**PATIENTS AND METHODS**

**Patients** This retrospective study was performed in accordance with the guidelines for the care for human study adopted by the ethics committee of the Hokkaido University Hospital (approved number: 016-0476). Patients’ information was obtained from daily medical records. A total of 50 patients aged over 20 years with advanced NSCLC who were administered carboplatin (area under the curve; AUC = 5–6) plus PTX (200 mg/m²) (plus bevacizumab 15 mg/kg, if non-squamous) every 3–4 weeks were enrolled. Patients administered bevacizumab were included since it has been reported that its administration in combination with carboplatin and PTX does not affect the incidence and severity of P-APS. Patients were divided into two groups; the NSAIDs group, which included patients who were administered NSAIDs routinely (more than half of usual daily dose) for pain or fever at least one day prior to PTX injection and were continued to be administered NSAIDs during the first cycle of chemotherapy from January 2008 to January 2012 and a control group with patients who were not administered NSAIDs at the beginning of first chemotherapy injection from September 2008 to March 2011. All patients who met the criteria in the surveillance period were enrolled. All of the enrolled patients had sufficient bone marrow, renal or liver function and 0 to 2 performance status. Patients with uncontrolled pain or regular administration of corticosteroids, narcotics, Shakuyaku-Kanzo-To, and gabapentin at the beginning of the chemotherapy, and whose purpose of NSAIDs administration were unknown were excluded. Patients with prophylactic administration of dexamethasone for several days after the chemotherapy against nausea and vomiting were also excluded.

**Survey of the Incidence, Severity, and Duration of P-APS** Incidence, severity, and duration of P-APS at the first cycle were retrospectively evaluated. The severity of P-APS was graded by physicians in accordance with the Common Terminology Criteria for Adverse Events version 4.0. The duration of P-APS was defined as the number of days from the appearance until the disappearance of symptoms such as myalgia and arthralgia. 

**Statistical Analysis** We hypothesized that the incidence of P-APS would reach 80% in control group, and 35–40% in the NSAIDS group. A required sample size was calculated to be 22–27 subjects per group to achieve 80% power with an alpha error of 5%. Twenty five patients were analyzed in each group since the number of the patients who fulfilled the criteria in NSAIDs group was twenty five.

The differences of patient characteristics in the NSAIDs and control groups were assessed using Fisher’s exact probability test for the categorical outcome variables and Mann-Whitney U test for the continuous parameters. Incidence of P-APS was compared using Fisher’s exact probability method, and severity of P-APS was assessed using Mann-Whitney U test. Comparison of the duration of P-APS be-
Patients in the NSAIDs group were administered loxoprofen sodium at baseline (Supplemental Table 1). There was no patient administered tramadol or supplementary analgesics such as pregabalin, duloxetine, or amitriptyline during the study period.

**RESULTS**

Patient Characteristics The clinical characteristics of the patients are summarized in Table 1. There were no significant differences in gender, age, clinical stage, performance status, presence of bone metastasis, body surface area (BSA), body mass index (BMI), serum creatinine level, liver dysfunction (grade 1 or more aspartate aminotransferase or alanine aminotransferase or γ-glutamyltransferase elevation) at the baseline, PTX dosage, and co-administration of bevacizumab between NSAIDs and control groups. Patients in the NSAIDs group were prescribed NSAIDs for pain (17 of 25, 68%) or fever (8 of 25, 32%). Approximately sixty percent of the patients in NSAIDs group were administered loxoprofen sodium at baseline (Supplemental Table 1). There was no patient administered tramadol or supplementary analgesics such as pregabalin, duloxetine, or amitriptyline during the study period.

Incidence and Site of P-APS Incidence of P-APS was 72% (18 of 25) in the control group and 84% (21 of 25) in the NSAIDs group (Table 2). The most frequent site of P-APS was the lower extremity; and this was reported in 18 of 25 (all of the patients who experienced P-APS) patients in the control group and 20 of 25 (95.2% of the patients who experienced P-APS) in the NSAIDs group. Approximately 20% of the patients experienced P-APS in the entire body. There was no difference in the site of P-APS between the two groups.

Severity and Duration of P-APS Table 3 shows the severity and duration of P-APS. Although P-APS in the NSAIDs group tended to be more severe than that in the control group, there was no significant difference between the two groups. The duration of P-
APS was $4.67 \pm 2.30$ d (from day $3.33 \pm 0.77$ to day $8.00 \pm 1.94$) in the control group and $6.19 \pm 3.30$ d (from day $3.10 \pm 0.70$ to day $9.29 \pm 3.15$) in the NSAIDs group. It was suggested that patients in the NSAIDs group tended to have longer P-APS than those in the control group; however, the duration was not significantly different between the two groups.

**Relationship of the Appearance of P-APS with Previous Pain** As shown in Table 2, approximately 80% of the patients previously administered NSAIDs experienced P-APS. About 90% of the patients administered NSAIDs due to previous pain experienced P-APS (Fig. 1). Moreover, in approximately half of patients administered NSAIDs for previous pain, the original pain deteriorated by P-APS (9 of 17, 52.9%). Whereas, three-fourths of patients with NSAIDs for fever had experienced P-APS.

**Rescue Administration against P-APS** Table 4 shows the additional analgesic medication administered for P-APS. In both groups, NSAIDs were primarily and most frequently administered to deal with P-APS. In the NSAIDs group, additional NSAIDs were administered once or twice a day (data not shown). Acetaminophen was significantly more frequently administered in the NSAIDs group. Some of the patients experienced severe P-APS and non-effectiveness of additional NSAIDs and/or acetaminophen, therefore, required to use narcotics.

The refractory rate of primarily additional NSAIDs administration for P-APS was not significantly different between the two groups. However, patients who were previously administered NSAIDs tended to experience less effects and required other medication.

**Adverse Effects Caused by Chemotherapy in the First Cycle** Table 5 shows the adverse effects (except P-APS) caused by carboplatin plus PTX with or without bevacizumab. Incidence of all or G3/4 severe adverse effects was almost similar between the two groups.

**Correlation between Patient Characteristics and the Incidence of P-APS** Univariate analysis for the search of risk factors for the incidence of P-APS suggested that there is no correlation between patient characteristics and the incidence of P-APS as with a previous report (Table 6). In addition, it was also revealed that symptoms which need NSAIDs administration did not affect P-APS. Multivariate analysis also revealed that there were no risk factors for the P-APS incidence.
**Table 5. Incidence of Adverse Effects except P-APS**

| Effect                  | Control group \((n = 25)\) | NSAIDs group \((n = 25)\) | \(p\)-value |
|-------------------------|----------------------------|----------------------------|-------------|
| Leukopenia              | All 24                     | 21                         | 0.35        |
|                         | G3/4 11                     | 9                          | 0.77        |
| Neutropenia             | All 24                     | 22                         | 0.61        |
|                         | G3/4 21                     | 17                         | 0.32        |
| Febrile neutropenia     | 2                          | 4                          | 0.67        |
| Anemia                  | All 22                     | 22                         | 1.00        |
|                         | G3/4 1                      | 2                          | 1.00        |
| Thrombopenia            | All 7                      | 6                          | 1.00        |
|                         | G3/4 0                      | 0                          | 1.00        |
| Nausea                  | All 5                      | 9                          | 0.35        |
|                         | G3/4 0                      | 0                          | 1.00        |
| Anorexia                | All 15                     | 16                         | 1.00        |
|                         | G3/4 2                      | 1                          | 1.00        |

**DISCUSSION**

PTX is one of the most important chemotherapeutic agents for NSCLC. P-APS occurs 1 to 3 d after PTX administration and resolves within a week. Even though the duration of P-APS is less than a week, it sometimes significantly reduces the patient’s quality of life and induces dose reduction of this medicine. It is important to study the efficacy of supportive care and risk factors for chemotherapy-induced adverse effects for the management of chemotherapy. As there is little data regarding P-APS incidence, prevention, and coping methods, and patients with breast and pancreatic cancer which paclitaxel is usually administered in their treatment are increasing, data about risk factors and coping strategy is important for appropriate and quick self-medication especially in outpatient chemotherapy.

It has been reported that P-APS is caused by nociceptor sensitization based on patient’s descriptions of pain and that rats administered PTX develop nerve injury within 24 h.\(^7\) It has also been reported that prostanoids might be related to P-APS.\(^{13,18-20}\) The analgesic effect of NSAIDs is caused by the inhibition of the action of cyclooxygenase (COX) and reduction in production of prostanoids. Therefore, it was hypothesized that they might affect P-APS. In this study, we evaluated the incidence, severity, and duration of P-APS between patients who were administered NSAIDs due to previous pain or fever prior to chemotherapy that included PTX and patients without prior administration of NSAIDs.

There was no difference in the incidence, severity, and duration of P-APS between the NSAIDs and control groups, although patients who had already been administered NSAIDs tended to have longer and more severe P-APS than those in the control group, suggesting that previous pain or inflammation was enhanced by PTX administration. In clinical, we sometimes experience that patients with rheumatoid arthritis, other arthritis, chronic low back pain get more pain at the same site by P-APS. Since approximately half of the patients who were previously administered NSAIDs for pain experienced stronger pain at the original site in this study and tumor fever suggests the existence of inflammation caused by tumor, it might be possible to speculate that patients with inflammation manifesting as symptoms such as pain or fever experience more severe P-APS.

Moreover, it has been shown that it is difficult to prevent the incidence of P-APS using corticosteroids although they have stronger anti-inflammatory action than NSAIDs as inflammation caused by 200 mg/m\(^2\) PTX is intense.\(^{10}\) It has also been reported that P-APS occurs in dose-related manner,\(^5\) it might be possible to conjecture that P-APS could occur less in previously NSAIDs administered patients in weekly PTX of 80–100 mg/m\(^2\).

It was also revealed that there are no risk factors regarding the incidence of P-APS, which was consistent with a previous report.\(^5\) These results are useful in explaining P-APS to patients prior to PTX administration and speculating about the incidence and duration of P-APS. However, we have evaluated how patient’s background such as previous pain or fever which need NSAIDs administration affects P-APS, not that whether NSAIDs have preventive effect against P-APS in this study. Further studies are needed to assess the preventive effect of NSAIDs against P-APS with non-previously NSAIDs administered patients.

NSAIDs, acetaminophen, pentazocine, corticosteroids, and narcotics were administered as rescue dose against P-APS. NSAIDs were primarily and most frequently administered in both groups, and acetaminophen was significantly more frequently ad-
Table 6. Univariate and Multivariate Analyses of the Risk Factors for P-APS

| P-APS incidence (n) | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value               |
| Gender              |                     |                       |                       |
| Male                | 28                  |                       | 0.25 (0.03–2.23)     | 0.22                  |
| Female              | 11                  |                       | 0.29 (0.03–2.82)     | 0.29                  |
| Age (years)         |                     |                       |                       |
| ≥ 70                | 8                   |                       | 0.69 (0.15–3.20)     | 0.63                  |
| < 70                | 31                  |                       |                       |                       |
| Performance status  |                     |                       |                       |                       |
| 0                   | 38                  |                       | —                    | —                    |
| 1                   | 1                   |                       | —                    | —                    |
| Staging             |                     |                       |                       |                       |
| 3B                  | 12                  |                       |                       |                       |
| 4 or recurrence     | 27                  | 0.50 (0.09–2.67)      | 0.42                  |
| Bone metastasis     |                     |                       |                       |                       |
| Yes                 | 9                   |                       | 0.80 (0.17–3.66)     | 0.77                  |
| No                  | 30                  |                       |                       |                       |
| Coadministration of NSAIDs |       |                       |                       |                       |
| Yes                 | 21                  | 2.04 (0.51–8.12)      | 0.31                  |
| No                  | 18                  |                       |                       |                       |
| Previous pain       |                     |                       |                       |                       |
| Yes                 | 15                  |                       |                       |                       |
| No                  | 24                  | 1.67 (0.38–7.29)      | 0.50                  |
| BSA (m²)            |                     |                       |                       |                       |
| ≥ 1.7               | 13                  | 0.42 (0.11–1.62)      | 0.21                  |
| < 1.7               | 26                  |                       | 0.80 (0.15–4.28)     | 0.79                  |
| BMI (kg/m²)         |                     |                       |                       |                       |
| ≥ 25                | 4                   |                       |                       |                       |
| < 25                | 35                  | 0.30 (0.06–1.64)      | 0.17                  |
| Renal dysfunction   |                     |                       |                       |                       |
| Yes                 | 5                   |                       | 0.38 (0.05–2.88)     | 0.35                  |
| No                  | 34                  | 0.66 (0.11–3.99)      | 0.65                  |
| Liver dysfunction   |                     |                       |                       |                       |
| Yes                 | 13                  | 1.33 (0.30–5.88)      | 0.70                  |
| No                  | 26                  |                       |                       |                       |

ministered in the NSAIDs group than in the control group. The refractory rate of primarily additional NSAIDs was not significantly different. However, patients who were previously administered NSAIDs tended to need other analgesics more often. These results suggest that it might be better not to use NSAIDs for P-APS in patients who were previously administered NSAIDs in terms of the overdose administration.

Analgesic effect of additional acetaminophen was obtained in four out of seven of the patients, and efficacy of narcotics was confirmed in one third of the patients in this study. Therefore, we are supposed to consider other analgesics such as acetaminophen, tramadol or narcotics as first rescue in such cases. Further studies are needed to confirm these results and hypotheses.

This is the first report that shows how clinical condition that needs NSAIDs or previously administered NSAIDs affects P-APS. As previously mentioned, since many patients with cancer need NSAIDs due to their pain and/or fever, the results obtained in this study could help in clinical practice and in the development of new prophylactic or treatment methods.

There are some limitations in the evaluation of the influence of previously administered NSAIDs on P-APS. First, this study was a retrospective study with a relatively small population of patients. It was re-
revealed that NSAIDs relieve P-APS in 60% of the P-APS experienced patients without previously NSAIDs administration in our preliminary retrospective investigation, and this rate was similar to the result in this study. We have calculated sample size from our hypothesis based on this result; 80% of the patients in control group experience P-APS, and previously NSAIDs administration reduces 60% of the P-APS incidence. However, the results obtained in this study were different from our hypothesis; incidence of P-APS was similar between the groups, whereas, patients who had already been administered NSAIDs tended to have longer and more severe P-APS than those in the control group. It could be possible to surmise that inflammation prior to PTX injection may have worsened the symptoms more than attenuating effect of NSAIDs. However, we did not evaluate NSAIDs prophylaxis in patients without pain and/or fever, and patients who need analgesics for their pain or fever but not administered in this study, therefore, it is difficult to assess the hypothesis described above.

Large-scale prospective cohort study is necessary to verify these results. Moreover, it is better to evaluate P-APS caused by single PTX administration since carboplatin might affect P-APS although its possibility is unlikely. Third, evaluation of the other PTX dose and in multiple administration should be conducted.

Finally, it was found that clinical condition that needs NSAIDs and previously administered NSAIDs prior to PTX injection do not affect the incidence, severity, and duration of P-APS.

Conflict of Interest  
YS, TY, MK, JS, NS, HD, KI have no conflict of interest. IK has received research funding for therapeutical trial from Bristol-Myers Squibb.

Supplementary Materials  
Supplementary materials are included in online version of this manuscript.

REFERENCES

1) Ohe Y., Ohashi Y., Kubota K., Tamura T., Nakagawa K., Negoro S., Nishiwaki Y., Saijo N., Ariyoshi Y., Fukuoka M., *Ann. Oncol.*, **18**, 317–323 (2007).

2) Niho S., Kunitoh H., Nokihara H., Horai T., Ichinose Y., Hida T., Yamamoto N., Kawaihara M., Shinkai T., Nakagawa K., Matsui K., Negoro S., Yokoyama A., Kudoh S., Kiura K., Mori K., Okamoto H., Sakai H., Takeda K., Yokota S., Saijo N., Fukuoka M., *Lung Cancer*, **76**, 362–367 (2012).

3) Rowinsky E. K., Chaudhry V., Forastiere A. A., Sartorius S. E., Ettinger D. S., Grochow L. B., Lubejko B. G., Cornblath D. R., Donehower R. C., *J. Clin. Oncol.*, **11**, 2010–2020 (1993).

4) Onetto N., Canetta R., Winograd B., Catane R., Dougan M., Grechko J., Burroughs J., Rozencweig M., *J. Natl. Cancer Inst. Monogr.*, **15**, 131–139 (1993).

5) Kunitoh H., Saijo N., Furuse K., Noda K., Ogawa M., *Br. J. Cancer*, **77**, 1686–1688 (1998).

6) Loprinzi C. L., Reeves B. N., Dakhil S. R., Sloan J. A., Wolf S. L., Burger K. N., Kamal A., Le-Lindqwister N. A., Soori G. S., Jaslowki A. J., Novotny P. J., Lachance D. H., *J. Clin. Oncol.*, **29**, 1472–1478 (2011).

7) Loprinzi C., Maddocks-Christianson K., Wolf S., Rao R., Dyck P., Mantyh P., Dyck P., *Cancer J.*, **13**, 399–403 (2007).

8) Fernandes R., Mazzarello S., Hutton B., Shorr R., Majeed H., Ibrahim M. F., Jacobs C., Ong M., Clemons M., *Support. Care Cancer*, **24**, 3633–3650 (2016).

9) Markman M., Kennedy A., Webster K., Kulp B., Peterson G., Belinson J., *Gynecol. Oncol.*, **72**, 100–101 (1999).

10) Saito Y., Kobayashi M., Yamada T., Sakakibara-Konishi J., Shinagawa N., Kinoshita I., Dosaka-Akita H., Iseki K., *Support. Care Cancer*, 2019. doi:10.1007/s00520-019-04808-y

11) Savarese D., Boucher J., Corey B., *J. Clin. Oncol.*, **16**, 3918–3919 (1998).

12) Yoshida T., Sawa T., Ishiguro T., Horiba A., Minatoguchi S., Fujiwara H., *Support. Care Cancer*, **17**, 315–320 (2009).

13) Nguyen V. H, Lawrence H. J., *J. Clin. Oncol.*, **22**, 1767–1769 (2004).

14) Jacobson S. D., Loprinzi C. L., Sloan J. A., Wilke J. L., Novotny P. J., Okuno S. H., Jatoi A., Moynihan T. J., *J. Support. Oncol.*, **1**, 274–278 (2003).

15) Eisenhauer E. A., ten Bokkel Huinink W. W., Swenerton K. D., Gianni L., Myles J., van der
Burg M. E., Kerr I., Vermorken J. B., Buser K., Colombo N., *J. Clin. Oncol.*, **12**, 2654–2666 (1994).

16) Kosmidis P., Mylonakis N., Skarlos D., Samantas E., Dimopoulos M., Papadimitriou C., Kalophonos C., Pavlidis N., Nikolaidis C., Papaconstantinou C., Fountzilas G., *Ann. Oncol.*, **11**, 799–805 (2000).

17) Moulder S. L., Holmes F. A., Tolcher A. W., Thall P., Broglio K., Valero V., Buzdar A. U., Arbuck S. G., Seidman A., Hortobagyi G. N., *Cancer*, **116**, 814–821 (2010).

18) Murata T., Ushikubi F., Matsuoka T., Hirata M., Yamasaki A., Sugimoto Y., Ichikawa A., Aze Y., Tanaka T., Yoshida N., Ueno A., Ohishi S., Narumiya S., *Nature*, **388**, 678–682 (1997).

19) Samad T. A., Sapirstein A., Woolf C. J., *Trends Mol. Med.*, **8**, 390–396 (2002).

20) Moriyama T., Higashi T., Togashi K., Iida T., Segi E., Sugimoto Y., Tominaga T., Narumiya S., Tominaga M., *Mol. Pain*, **1**, 3 (2005).