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〔Original Short Communication〕

A retrospective study on naproxen, rather than loxoprofen, for cancer pain

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Abstract

Nonsteroidal anti-inflammatory drugs（NSAIDs）are recommended by the World Health Organization for the treatment of cancer pain. In Japan, loxoprofen is the most commonly used drug among a variety of NSAIDs. However, our palliative care team（PCT）switched from loxoprofen to naproxen, a long-acting NSAID, for cancer pain. Consequently, our clinical impression was that the pain score was often improved. Therefore, we investigated whether switching from loxoprofen to naproxen reduced cancer pain.

A retrospective medical record survey was conducted. In a total of 119 inpatients who consulted the PCT from April 2018 to February 2019 in the Tokyo Medical University Hospital, 10 cases were enrolled in this study. We first switched the prescribed NSAID loxoprofen to naproxen for these patients. Furthermore, the mean numerical rating scale（NRS）scores, body temperatures, opioid prescriptions, and numbers of rescue doses were recorded on the days before and after switching the drugs.

Consequently, the means of the NRS scores before and after switching the NSAIDs were 3.50±1.62（mean±SD）（range: 1.7-6.5）and 1.15±1.48（0-3.67）（$p<0.001$, using the paired t-test）, respectively.

Moreover, no statistical differences were noted on the other survey variables（$p>0.05$）.

In conclusion, compared with loxoprofen, naproxen may be effective in reducing mild-to-moderate cancer pain.

***Key words*: cancer pain, nonsteroidal anti-inflammatory drug, naproxen, loxoprofen**

Pain is one of most common and difficult symptoms in cancer; thus, its management is extremely important [1]. It is experienced by 20%-50% of patients with cancer at diagnosis and by up to 60%-90% in those with cancer at an advanced stage[2].

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Nonsteroidal anti-inflammatory drugs（NSAIDs）are recommended by the World Health Organization for the treatment of cancer pain[3]. In Japan, loxoprofen is the most commonly used NSAID[4]. However, the appropriate type of NSAID for treating cancer pain is yet to be established[5].

Existing literature indicates that naproxen（750-1,100 mg/day）is not superior to diclofenac（200 mg/day）, indomethacin（150 mg/day）, or aspirin（2400 mg/day）[6-8]. Additionally, in Japan, the maximum

dosages of naproxen and loxoprofen are 600 mg/day (Interview form of naproxen: https://www.mhlw.go.jp/content/11121000/000342038.pdf) and 180 mg/day, respectively (Interview form of loxoprofen:https://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000065373.pdf). However, no comparative studies between these two drugs, at the doses used in Japan, have been conducted with respect to treating cancer pain.

Therefore, we conducted a retrospective survey to investigate the effectiveness of switching from 180 mg of loxoprofen to 600 mg of naproxen, in reducing cancer pain.

In this study, we aimed to determine whether 600 mg/day of naproxen decreases the mean numerical rating scale (NRS) scores in inpatients with cancer pain compared with the prescribed loxoprofen dosage of 180 mg/day. The secondary aims were to investigate the needed rescue doses of opioids and body temperature after switching from loxoprofen to naproxen.

The clinical records of 119 inpatients who consulted the palliative care team (PCT) for cancer pain at the Tokyo Medical University Hospital, Japan, from April 2018 to February 2019 were retrospectively reviewed. Consequently, 10 of them who were prescribed loxoprofen and had this NSAID switched to naproxen by the PCT, because the PCT evaluated that switching NSAIDs was appropriate for mild-to-moderate pain, were enrolled. At the day of switching NSAIDs, 600 mg of naproxen were administered.

The following demographic clinical data were collected: gender, age, cancer type, prescribed opioid, and pain site. In addition, the means of NRS (at least 3 times a day), number of rescue analgesics for pain relief, and body temperatures before and after switching from loxoprofen to naproxen were compared. Only the before and after days were selected because more factors (e.g., cancer growths, other drugs, physical conditions) can influence the NRS scores.

The statistical analysis of data was performed using the paired t-test with Prism 4 for Macintosh. P values of <0.05 were considered statistically significant, and the results were expressed as the mean ± standard deviation.

Of the 10 inpatients who were enrolled in this study, 80% were males (n = 8), and 20% were females (n = 2), with their ages ranging from 49 to 85 years old. In addition, the diagnoses were as follows" cancers of the lung (n = 2), esophagus (n = 1), thyroid (n = 3), pancreatic (n = 3), and bile duct (cholangiocarcinoma) (n = 1). Furthermore, the pain sites include the neck (owing to bone metastasis) (n = 3), upper limb (owing to neuropathic pain) (n = 1), chest (owing to bone metastasis) (n = 1), abdomen (owing to visceral pain) (n = 4), and back (owing to bone metastasis) (n = 1). Seven patients using opioids were also observed: slow-release oxycodone (10-20 mg/day) (n = 5), morphine sulfate (20 mg/day) (n = 1), and transdermal fentanyl (4 mg/day) (n = 1). Each rescue dose was set at 10～20% of the daily opioid consumption, except for fentanyl buccal (100 microgram/time). Additionally, there were 3 patients who were not using opioids.

The mean NRS score on the day before switching the NSAIDs (i.e., from loxoprofen [180 mg/day] to naproxen [600 mg/day]) was 3.50 ± 1.62 (range, 1.7-6.5), whereas that on the day after switching the NSAID was 1.15 ± 1.48 (0-3.67) ($p<0.001$). (Fig. 1) Further, the mean of the difference was 2.35 (95% confidence intervals, 1.64-3.07).

The numbers of rescue doses administered on the days before and after switching the NSAIDs were 2.3 ± 3.3 and 2.1 ± 3.5/day ($p>0.05$), respectively.

The mean body temperatures on the days before and after switching the NSAIDs were 36.7 ± 0.2 and 36.8 ±

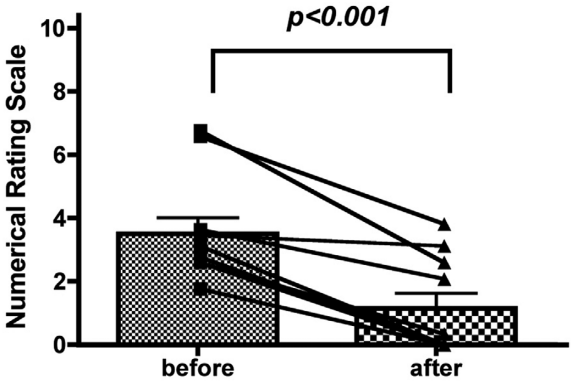

Fig. 1 Mean NRS scores on the days before and after switching from loxoprofen to naproxen. The mean NRS scores before and after were 3.50 ± 1.62 and 1.15 ± 1.48 ($p<0.001$, using the paired t-test), respectively.

0.31 ($p > 0.05$) ℃, respectively.

No adverse events of naproxen were noted during the period (e.g. acute drug allergic reaction, gastrointestinal disorder, and bleeding).

To the best of our knowledge, this is the first report describing the effectiveness of switching 180 mg/day of loxoprofen as the prescribed NSAID to 600 mg/day of naproxen in reducing cancer pain. A statistically significant decrease in the group difference of the mean NRS scores was noted after switching from loxoprofen to naproxen ($p < 0.001$). In addition, no significant difference in the number of rescue doses was found ($p > 0.05$). Therefore, these findings suggest that switching from loxoprofen to naproxen is effective in reducing any type of cancer pain.

Although naproxen is often used for tumor fever [9], this study showed that no significant differences were noted in the body temperatures after switching the NSAID because the patients were afebrile.

Clinically, loxoprofen is often prescribed because of its prodrug property that reduces gastrointestinal complications. In addition, its half-life ($T_{1/2}$) is 2.2 h, whereas that of naproxen is 14 h. End-of-dose failure in opioids is well known; therefore, controlled-release opioids are recommended for sustained cancer pain management, except for breakthrough pain[10,11]. Therefore, our results suggest that NSAIDs with long half-lives are suitable for the reduction of cancer pain. Previous comparative studies of naproxen and other NSAIDs, which indicated that naproxen was not superior to other NSAIDs, were studied at the greater doses than that used in Japan, i.e., almost double doses (e.g., in Japan, 75 mg is administered for indometacin and dicrofenac). There are no comparative studies of the differences of drug potency between loxoprofen and naproxen, especially at the doses used in Japan, therefore, the comparison of clinical doses we can use safely is important.

Our study has some limitations. First, in this study, a retrospective medical record survey was conducted. At the time of the PCT's first action, biases may be present because the PCT evaluated that switching only NSAIDs was appropriate for mild-to-moderate pain (range of mean NRS scores: 1.7-6.5). Thus, the finding may not be applicable to patients with severe cancer pain.

Second, a comparison of this current study with one involving the switch of naproxen to loxoprofen has not yet been elucidated.

In conclusion, naproxen may be effective in reducing mild-to-moderate cancer pain. However, further clinical trials are needed to confirm the result.

Contributors

OS designed the study, wrote the initial draft, analyzed and interpreted of the manuscript. AM has contributed to data collection and interpretation, and critically reviewed the manuscript. AM approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This study was approved by the Institutional Review Board of Tokyo Medical University Hospital, Japan (T2019-0058). Informed consents were obtained in the form of opt-out on the web-site of Tokyo Medical University Hospital.

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