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Effects of Gabapentin on Brain Hyperactivity Related to Pain and Sleep Disturbance Under a Neuropathic Pain-Like State Using fMRI and Brain Wave Analysis

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KEY WORDS neuropathic pain; fMRI; EEG; gabapentin; chronic pain

ABSTRACT Neuropathic pain is the most difficult pain to manage in the pain clinic, and sleep problems are common among patients with chronic pain including neuropathic pain. In the present study, we tried to visualize the intensity of pain by assessing neuronal activity and investigated sleep disturbance under a neuropathic pain-like state in mice using functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG)/electromyogram (EMG), respectively. Furthermore, we investigated the effect of gabapentin (GBP) on these phenomena. In a model of neuropathic pain, sciatic nerve ligation caused a marked decrease in the latency of paw withdrawal in response to a thermal stimulus only on the ipsilateral side. Under this condition, fMRI showed that sciatic nerve ligation produced a significant increase in the blood oxygenation level-dependent (BOLD) signal intensity in the pain matrix, which was significantly decreased 2 h after the i.p. injection of GBP. Based on the results of an EEG/EMG analysis, sciatic nerve-ligated animals showed a statistically significant increase in wakefulness and a decrease in nonrapid eye movement (NREM) sleep during the light phase, and the sleep disturbance was almost completely alleviated by a higher dose of GBP in nerve-ligated mice. These findings suggest that neuropathic pain associated with sleep disturbance can be objectively assessed by fMRI and EEG/EMG analysis in animal models. Furthermore, GBP may improve the quality of sleep as well as control pain in patients with neuropathic pain. **Synapse 65:668–676, 2011.**

INTRODUCTION

Neuropathic pain can be defined as pain resulting from lesions or diseases of the sensory transmission pathways in the peripheral or central nervous system, and is characterized by pain and sensory abnormalities in body areas that have lost their normal sensory innervation (Troels and Nanna, 2009). It is caused by dysfunctions in the peripheral or central nervous

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system without peripheral nociceptive stimulation. Many common diseases, such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, spinal cord injury, cancer, stroke, and degenerative neurological diseases, may produce neuropathic pain. Multiple mechanisms, including changes in the peripheral nervous system, spinal cord, brainstem or brain, may contribute to neuropathic pain (Ro and Chang, 2005). To date, several animal models of chronic pain have been created to investigate the mechanisms that underlie the development of neuropathic pain (Beiche et al., 1998; Goppelt-Struebe and Beiche, 1997). Based on previous studies with these animal models, it has long been considered that cellular and molecular events within the spinal cord and/or dorsal root ganglia (DRG) play important roles in neuropathic pain.

In a clinical setting, it is important to first assess the intensity of pain felt by patients to understand the cause of their pain and judge the effect of any treatment. However, it is very difficult to assess the intensity of pain because pain is essentially a subjective experience. Recently, while it has been shown that pain can be assessed more objectively with the use of Pain Vision® (NIPRO CO Ltd., Osaka, Japan), which judges the intensity of pain by a low electric current, the degree of pain is typically assessed subjectively through the use of various approaches, including the visual analog scale (VAS), numerical rating scale (NRS), verbal rating scale, and face scale. Therefore, a method is urgently needed to realize the objective assessment of the intensity of pain.

The nociceptive signals to the central nervous system are transmitted primarily by small myelinated (Aδ) and unmyelinated (C) sensory afferent fibers to the substantia gelatinosa in the dorsal horn, with further rostral spread to the ventral-posterior nucleus of the thalamus (Craig, 1996; Han et al., 1998). Furthermore, nociceptive information is transmitted by a neuronal pathway projecting from the thalamus to the so-called pain matrix, which includes the somatosensory cortex (S1) and cingulate cortex (CG). While neuropathic pain may result from hypersensitivity because of the alteration of these primary afferent neurons and/or spinal dorsal horn neurons following nerve injury (Ji and Woolf, 2001), there have been few reports on the hypersensitivity of sensory neurons following nerve injury that would lead to the direct activation of ascending pain transmission in animal models. Interestingly, functional magnetic resonance imaging (fMRI) can be used to objectively evaluate pain perception in the central nervous system in healthy subjects and in those with various kinds of pain (Honore et al., 2000; Zhang et al., 2004). Noxious heat stimulation in humans or repetitive heat stimulation through peltier elements in animals has been shown to activate several brain regions (Becerra et al., 1999; Wise et al., 2002, 2004). Recently, it has been demonstrated that neuroimaging in humans and animals can be used to detect changes in regional activation initiated by noxious stimulation or the administration of drugs that modulate pain (Honey et al., 2008; Leslie and James, 2000; Shih et al., 2008), which shows that fMRI is useful for objectively investigating the mechanism of neuropathic pain related to the activation of ascending pain pathways in animal models.

Patients with chronic pain also commonly experience sleep disturbance (Atkinson et al., 1988; Morin et al., 1998; O'Brien et al., 2010; Pilowsky et al., 1985), and the treatment of such sleep disturbance may be beneficial in these patients (O'Brien et al., 2010). It has been reported that sleep problems and daytime sleepiness are common among opioid-treated primary care patients with chronic pain and seem to be related mainly to depression and the severity of pain (Zgierska et al., 2007). Therefore, in the present study, we tried to visualize the intensity of pain by assessing neuronal activity under a neuropathic pain-like state in mice using the fMRI assay and investigated sleep disturbance by using electroencephalogram (EEG)/electromyogram (EMG) recording. Furthermore, we evaluated the effect of gabapentin (GBP) on pain-related brain hyperactivation and its relation to sleep disturbance using both of these techniques.

Abbreviations

BOLD	blood oxygenation level-dependent
CG	cingulate cortex
DRG	dorsal root ganglia
EEG	electroencephalogram
EMG	electromyogram
EPI	echo planar imaging technique
fMRI	functional magnetic resonance imaging
GBP	gabapentin
lTH	lateral thalamic region
mTH	medial thalamic region
NREM	nonrapid eye movement
NRS	numerical rating scale
PMPS	postmastectomy pain syndrome
PTPS	postthoracotomy pain syndrome
REM	rapid eye movement
ROI	Regions of interest
VAS	visual analog scale.

MATERIALS AND METHODS

Animals

The present study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, as adopted by the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science and Technology of Japan. This study was approved by the Animal Research Committee of Hoshi University. C57BL/6J mice (weighing 18–23 g, 260 males) (CLEA Japan, Inc., Tokyo, Japan) were used for this study. Animals were kept in a room with an ambient temperature of 23°C ± 1°C and a 12-h light–dark cycle (lights on 8:00 a.m. to 8:00 p.m.). Food and water were available *ad libitum* during the experimental period. At the end of

the experiments, animals were humanely killed by a rising concentration of ethyl ether.

Neuropathic pain model

We produced a partial sciatic nerve injury by tying a tight ligature with a 8-0 silk suture around approximately one-third to one-half the diameter of the sciatic nerve on the right side (ipsilateral side) under a light microscope (SD30, Olympus, Tokyo, Japan) as described previously. In sham-operated animals, the nerve was exposed without ligation.

Measurement of thermal thresholds

Thermal and tactile thresholds were performed following the methods described previously. To assess the sensitivity to thermal stimulation, the right plantar surface of mice was tested individually using a well-focused radiant heat light source (model 33 Analgesia Meter; IITC/Life Science Instruments, Woodland Hills, CA). The intensity of the thermal stimulus was adjusted to achieve an average baseline paw-withdrawal latency of ~8–10 s in naive mice. The paw-withdrawal latency was determined as the average of three measurements per paw. Only quick hind paw movements (with or without licking of hind paws) away from the stimulus were considered to be a withdrawal response. Paw movements associated with locomotion or weight-shifting were not counted as a response. The paws were measured alternating between left and right with an interval of more than 3 min between measurements. Before the behavioral responses to the thermal stimulus were tested, mice were habituated for at least 30 min in a clear acrylic cylinder (15 cm high and 8 cm in diameter). Under these conditions, the latency of paw withdrawal in response to the thermal stimulus was tested. The data represent the average value for the paw withdrawal latency of the right hind paw.

Mild noxious heat stimulation

Contact heat stimulation was applied using a custom-made, computer-controlled peltier heating and cooling device. Peltier elements with a surface area of 8.3×8.3 mm^2 were fixed at the right hindpaw. Starting at a baseline of 34°C, a stimulation temperature of 43°C–46°C was reached after 18 s at 0.67°C/s. The stimulation temperature plateau was held for 20 s. Over the subsequent 22 s, the temperature was dropped linearly back to the baseline.

Functional magnetic resonance imaging (FMRI)

Experiments were performed with a Unity Inova spectrometer (Varian, Palo Alto, CA), which was interfaced to a 9.4-T/31-cm horizontal bore magnet equipped with actively shielded gradients capable of 300 mT/m in a risetime of 500 s (Magnex Scientific, Abingdon, UK). During the measurements, mice were slightly anesthetized with isoflurane (0.5%–1%). Mice were then transferred to a cradle designed to fit inside the probe of the MR system. A continuous fMRI scanning protocol was used to study changes in brain signal intensity using T2-weighted blood oxygenation level-dependent (BOLD) contrast.

A functional series was acquired using the Echo Planar Imaging Technique (EPI: matrix = 64 × 64, TR = 2000 ms, TE = 35 ms, 2 acquisitions, slice thickness = 1 mm, field of view = 25.6×25.6 mm^2). Anatomical scans with high spatial resolution were collected using a fast spin echo pulse sequence (matrix = 256 × 256, TR = 2000 ms, TE = 45 ms, slice thickness = 1 mm, field of view = 25.6×25.6 mm^2).

Sciatic nerve-ligated mice were lightly anesthetized with 0.75% of isoflurane at 7 days after surgery, and heat stimuli were applied to the right hindpaw. Likewise, to investigate the effect of a single intraperitoneal (i.p.) treatment with GBP, mice were lightly anesthetized with 0.75% isoflurane at 2 h after i.p. injection of GBP (60 mg/kg/mouse), and heat stimuli were applied to the right hindpaw.

Data analysis was carried out using FEAT (http://www.fmrib.ox.ac.uk) software packages. Z (Gaussianised T/F) statistic images were set up on the condition of $Z > 2.3$, with clusters with a significance threshold of $P = 0.05$. Regions of interest (ROI) were manually selected and statistical analyses were performed using ImageJ image-analysis software. ROI were drawn according to an atlas of the mouse brain. The BOLD signal intensity values in each ROI were extracted and normalized to the time of baseline (expressed as a percent change from baseline).

Electroencephalogram and electromyogram recordings

Under 3% isoflurane anesthesia, mice were implanted with electroencephalogram (EEG) and electromyogram (EMG) electrodes for polysomnographic recordings (Pinnacle Technology, Inc., KS). Briefly, to monitor EEG signals, two stainless-steel EEG recording screws were positioned 1 mm anterior to the bregma or lambda, both 1.5 mm lateral to the midline. EMG activity was monitored by stainless steel, teflon-coated wires placed bilaterally into both trapezius muscles. Sleep-wake states were then monitored for a period of 24 h, encompassing both the baseline and the experimental day. The EEG/EMG signals were amplified, filtered (EEG, 0.5–30 Hz; EMG, 20–200 Hz), digitized at a sampling rate of 128 Hz, and recorded by using SLEEPSIGN software (Kissei Comtec, Nagano, Japan). Vigilance was automatically classified off-line by 4-s epochs into three stages, i.e., wakefulness, rapid eye movement (REM), and non-

REM (NREM) sleep, by SLEEPSIGN according to the standard criteria. As a final step, defined sleep-wake stages were examined visually and corrected, if necessary. For each epoch, the EEG power density in the delta (0.75–4.0 Hz) and theta bands (6.25–9.0 Hz) and the integrated EMG value were displayed on a PC monitor. Three vigilance states—(1) waking (high EMG and low EEG amplitude and high theta activity concomitant with highest EMG values), (2) NREM sleep (low EMG and high EEG amplitude, high delta activity), and (3) REM sleep (low EMG and low EEG amplitude, high theta activity)—were determined for 4-s epochs and the scores were entered into a PC via a keyboard. EEG and EMG activities were monitored for 24 h at 7 days after sciatic nerve ligation. Recordings were started from 8:00 p.m. Saline or GBP was injected three times at 8:00 p.m. (saline or 60 mg/kg of GBP), 2:00 a.m. (saline or 60 mg/kg of GBP), and 8:00 a.m. (saline or 300 mg/kg of GBP).

Drugs

The drug used in this study was gabapentin (GBP: Sigma-Aldrich Co.). GBP was dissolved in 0.9% sterile physiological saline.

Statistical analysis

Data are expressed as the mean with SEM. The statistical significant of differences between the groups was assessed with one-way or two-way ANOVA following by the Bonferoni multiple comparisons test. All statistical analyses were performed with Prism version 5.0a (GraphPad Software, Inc., CA).

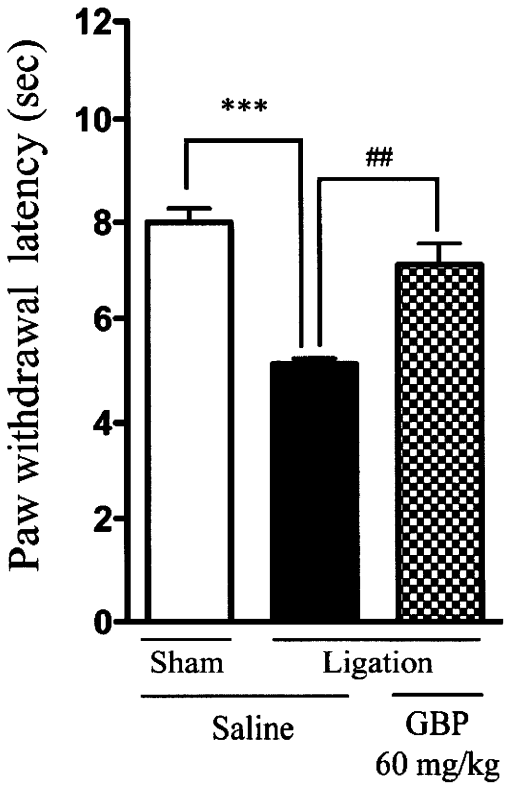

Fig. 1. Effect of gabapentin (GBP) on thermal hyperalgesia induced by nerve ligation in mice. Groups of mice were injected with GBP (60 mg/kg, i.p.) or saline at 7 days after sciatic nerve ligation or sham operation. Thermal hyperalgesia was measured 1 h after a single i.p. injection of GBP or saline treatment. One-way ANOVA was performed, followed by bonferroni testing. Each point represents the mean ± SEM of six to eight mice. ***$P < 0.001$ vs. sham with saline, ##$P < 0.01$ vs. nerve ligation with saline.

RESULTS

Thermal hyperalgesia induced by sciatic nerve ligation in mice

Sciatic nerve ligation caused a marked decrease in the latency of paw withdrawal in response to a thermal stimulus only on the ipsilateral side ($F_{(2,17)} = 17.11$, $P < 0.001$ vs. nerve-ligated mice with saline, Fig. 1). Such a persistent painful state caused by partial ligation of the sciatic nerve was suppressed by GBP ($F_{(2,17)} = 17.11$, $P < 0.001$ vs. nerve-ligated mice with saline). Under the present condition, GBP at the dose used did not show the acute antinociceptive effect in sham-operated mice (data not shown).

Changes in BOLD signal intensity under a neuropathic pain-like state using fMRI

We investigated the changes in BOLD signal intensity in sciatic nerve-ligated mice under 0.5%–1% isoflurane anesthesia using fMRI. BOLD signal intensity correlates with neuronal activity in pain. Sciatic nerve ligation produced a significant increase in BOLD signal intensity in the medial thalamic region (mTH, $F_{(1,12)} = 9.493$, $P < 0.01$), lateral thalamic region (lTH, $F_{(1,12)} = 4.993$, $P < 0.05$), cingulate cortex (CG, $F_{(1,12)} = 15.20$, $P < 0.01$), and somatosensory cortex (S1, $F_{(1,12)} = 50.27$, $P < 0.001$) compared to the sham operation (Fig. 2).

Changes in the analgesic effect of GBP under a neuropathic pain-like state using fMRI

Two hours after the i.p. injection of GBP in the sciatic nerve ligation groups, BOLD signal intensity was significantly decreased in the mTH ($F_{(1,12)} = 9.493$, $P < 0.01$), lTH, ($F_{(1,12)} = 4.993$, $P < 0.05$), CG ($F_{(1,12)} = 15.2$, $P < 0.01$), and S1 ($F_{(1,12)} = 50.27$, $P < 0.001$) compared to that with the injection of saline (Fig. 2B).

Changes in vigilance under a neuropathic pain-like state using EEG/EMG

Using this experimental model for neuropathic pain, we next investigated the changes in sleep patterns in sciatic nerve-ligated mice. Cerebral cortical activity and postural muscle tone, monitored by EEG/

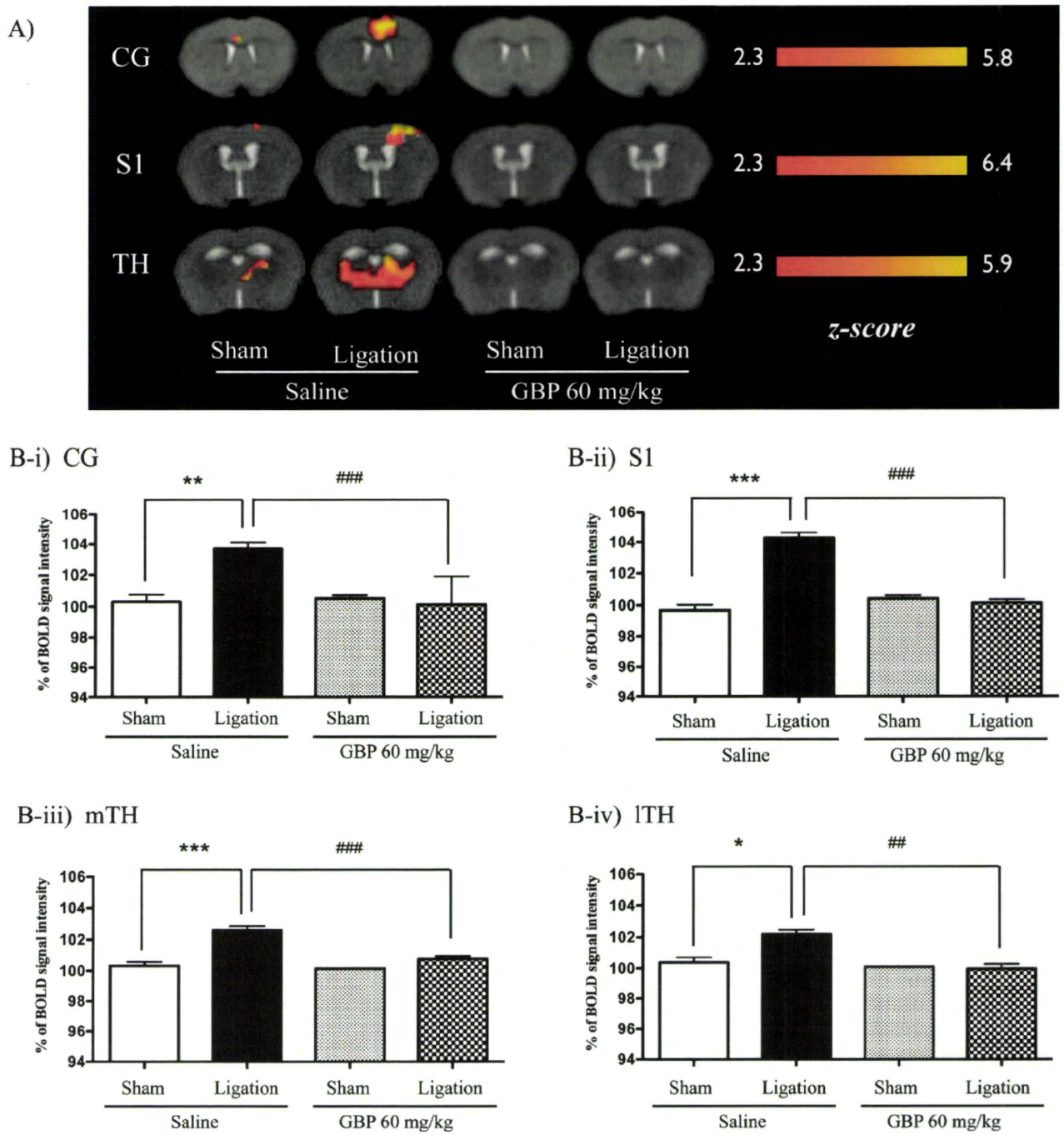

Fig. 2. Effect of gabapentin (GBP) on the increase in BOLD signal intensity induced by sciatic nerve ligation. A: BOLD signal intensity in the cingulate cortex (CG), somatosensory cortex (S1), and thalamic region (TH) was measured 60 min (CG), 80 min (S1), or 100 min (TH), respectively, after a single i.p. injection of GBP (60 mg/kg) or saline in sham-operated or sciatic nerve-ligated mice. GBP or saline was injected at 7 days after sciatic nerve ligaion or sham operation. B: BOLD signal intensity is expressed as percentages of the corresponding baseline levels with mean ± SEM for five mice. (B-i): CG, (B-ii) S1, and (B-iii) medial thalamic region (mTH); (B-i.v) lateral thalamic region (lTH). Two-way ANOVA was performed followed by bonferroni testing. Each bar represents the mean ± SEM of five mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. sham-operated mice with saline, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. nerve-ligated mice with saline.

EMG, are useful for discriminating sleep/wake abnormalities. Vigilance was classified offline into three stages: wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. Sciatic nerve ligation groups showed a statistically significant increase in wakefulness ($F_{(1,4)} = 17.55$, $P < 0.05$ vs. sham operated mice with saline) and a decrease in NREM sleep ($F_{(1,4)} = 23.24$, $P < 0.01$ vs. sham-operated mice

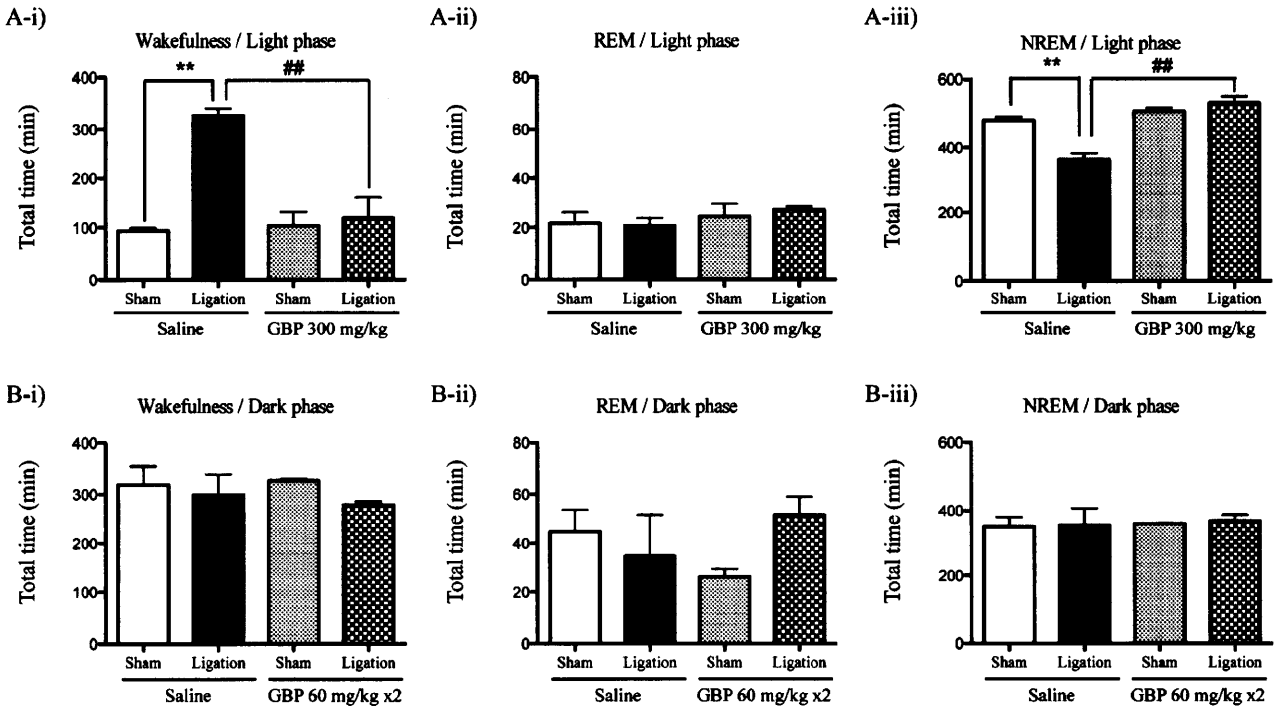

Fig. 3. Changes in sleep vigilance related to hypnotic effects of GBP under a neuropathic pain-like state as determined by EEG/EMG recordings. Sleep-wake states following saline or GBP injection at 7 days after sciatic nerve ligation. Saline or GBP was injected three times at 8:00 p.m. (saline or 60 mg/kg of GBP), 2:00 a.m. (saline or 60 mg/kg of GBP), and 8:00 a.m. (saline or 300 mg/kg of GBP). Total time spent in the wakefulness stage [in the light phase (A-i) and dark phase (B-i)], REM sleep stage [in the light phase (A-ii) and dark phase (B-ii)], and NREM sleep stage [in the light phase (A-iii) and in dark phase (B-iii)] was determined by EEG/EMG recording. Two-way ANOVA was performed followed by bonferroni testing. Each bar represents the mean ± SEM of five mice. $^{**}P < 0.01$ vs. sham operation with saline, $\#\#P < 0.01$ vs. nerve ligation with saline.

with saline) during the light phase (Fig. 3A). REM sleep during the light phase was not affected by sciatic nerve ligation. On the other hand, there was no significant difference in the sleep conditions during the dark phase between the two groups (Fig. 3B).

Changes in the hypnotic effects of GBP under a neuropathic pain-like state using EEG/EMG recording

To confirm the changes in the hypnotic effects of GBP under a neuropathic pain-like state, we performed EEG/EMG recording. The increased wakefulness and decreased NREM during the light phase were significantly attenuated by i.p. injection of GBP in nerve-ligated mice compared to those in sham-operated mice (wakefulness: $F_{(1,4)} = 17.55$, $P < 0.05$ vs. nerve-ligated mice with saline, NREM: $F_{(1,4)} = 23.24$, $P < 0.01$ vs. nerve-ligated mice with saline, Fig. 3).

DISCUSSION

Since cortical areas are activated by receiving noxious information through the spinothalamic tract, neuroimaging studies may be able to reveal their activities by demonstrating brain circuitry (Borsook et al., 2007; Jones et al., 1991; Talbot et al., 1991). These cortical representations of pain are called the pain matrix, which includes the S1, CG, and prefrontal cortex (Treede et al., 1999). Among these areas, the CG area is an affective-motivational component of pain and mainly receives information from the medial system of the spinothalamic tract (Melzack, 1999; Rorden and Karnath, 2004). On the other hand, the S1 area is a sensory-discriminative component of pain and mainly receives information from the lateral system of the spinothalamic tract. The mTH and lTH are also categorized as centers for pain perception and relay sensory information to those cortical areas. In the present fMRI study, we investigated the changes in BOLD signal intensity in several brain regions following the application of heat stimuli with the use of peltier elements tightly attached to the right hindpaws of nerve-ligated mice. Sciatic nerve-ligated mice with mild noxious stimulation under anesthesia exhibited a significant increase in the BOLD signal in the mTH, lTH, CG, and S1. Therefore, we propose here that "pain" may be memorized in the brain during an operation if analgesic drugs are not used, which results in the development of neuropathic pain in some cases. In fact, postthoracotomy pain syndrome (PTPS) (Hazelrigg et al., 2002; Karmakar and Ho, 2004; Koehler and Keenan, 2006) and postmastectomy pain syndrome

(PMPS) (Couceiro et al., 2009; Ramesh et al., 2009; Vecht et al., 1989) have been classified as neuropathic pain. Koehler et al. reported that PTPS brings psychological distress to the patient, and also has detrimental effects on pulmonary function and postoperative mobility, leading to increased morbidity. Therefore, aggressive perioperative and postoperative pain management is best achieved through the use of an epidural anesthetic and by covering breakthrough pain with an i.v.-PCA (Koehler and Keenan, 2006). Karmakar et al. reported that an aggressive multimodal perioperative pain management regimen should be commenced before the surgical incision to prevent PTPS. In PMPS, one of the most well-established risk factors for the development of phantom breast pain and other related neuropathic pain syndromes is severe acute postoperative pain, indicating that the relief of severe acute pain may reduce the risk of chronic pain (Ramesh et al., 2009). Therefore, it seems likely that aggressive multimodal perioperative pain management with analgesics is indispensable for preventing the development of chronic pain related to invasive surgery, regardless of whether or not patients are conscious.

GBP is a novel analgesic drug, which was originally developed as an anticonvulsant (Governo et al., 2008). GBP has little effect in models of acute nociception (Eckhardt et al., 2000; Hunter et al., 1997; Jun and Yaksh, 1998; Stanfa et al., 1997), but significantly attenuates hyperalgesia (Jones and Sorkin, 1998; Jun and Yaksh, 1998) and allodynia (Hwang and Yaksh, 1997) in neuropathic pain models (Chapman et al., 1998; Coderre et al., 2007; Field et al., 2000; Fox et al., 2003; Joshi et al., 2006; Ling et al., 2007; Lynch et al., 2004; Xiao et al., 2007). In the clinical setting, GBP is used to relieve many chronic pain states, including neuropathic pain (Attal et al., 2006; Backonja et al., 1998; Hempenstall et al., 2005; Iannetti et al., 2005; Rice and Maton, 2001; Rowbotham et al., 1998). GBP binds to the auxiliary $\alpha_2\delta$ subunit of voltage-sensitive calcium channels (Dooley et al., 2007; Gee et al., 1996). Although other mechanisms have also been proposed (Chizh et al., 2000; Shimoyama et al., 2000), $\alpha_2\delta$ subunits are likely to be important sites of action that underlie the analgesic effects of GBP (Governo et al., 2008). In the present study, increased BOLD signal intensity was almost absent in brain regions related to pain, including the mTH, lTH, CG, and S1 after i.p. injection of GBP in sciatic nerve-ligated mice, indicating that GBP almost completely suppressed the transmission of pain signals to their related regions after nerve injury.

Since GBP almost completely suppressed the transmission of pain signals to the CG area, which is related to an affective-motivational component of pain, we next investigated the effect of GBP on sleep disorder under a neuropathic pain-like state. Several clinical reports on chronic pain of various etiologies have shown that it significantly interferes with sleep (Atkinson et al., 1988; Galer et al., 2000a,b; Haythornthwaite et al., 1991; Moffitt et al., 1991; Morin et al., 1998; Nicholson and Verma, 2004; O'Brien et al., 2010; Pilowsky et al., 1985; Zgierska et al., 2007). In the present study, we demonstrated that wakefulness and NREM sleep are equally disturbed in sciatic nerve-ligated mice. It was previously reported that constriction of the sciatic nerve induced poor sleep quality with disrupted sleep in rats, particularly during the first week of that condition. In the present study, sleep dysregulation was observed 7 days after sciatic nerve ligation in mice. Under the present condition, a higher dose of i.p. GBP clearly improved such sleep disturbance during the light phase ("sleep period" for mice) in nerve-ligated mice. In contrast, the i.p. administration of GBP did not affect the sleep pattern during the dark phase ("waking period" for mice). Taken together, the present results indicate that treatment with adequate doses of GBP through the "waking-sleep" cycle is an effective method for patients to control pain and improve sleeping disturbance without affecting their daily life under a neuropathic pain-like state.

In conclusion, we successfully visualized the intensity of neuropathic pain in an animal model using fMRI in this study. Even if mice were under isoflurane anesthesia, sciatic nerve ligation along with the application of thermal noxious stimuli caused a significant increase in BOLD signal in brain regions related to pain. The increased BOLD signal intensity was dramatically decreased in the pain-matrix brain area of sciatic nerve-ligated mice after i.p. injection of GBP. In the EEG/EMG recording, increased wakefulness and decreased NREM sleep were clearly observed following sciatic nerve ligation. This sleep disturbance was also completely restored to the normal sleep condition by a relatively higher dose of GBP. These findings provide evidence that GBP is useful for improving the quality of sleep and for controlling pain in patients with neuropathic pain.

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がん疼痛に対するHFT-290の第Ⅲ相臨床試験
－用量換算検証試験－

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－Dose-Conversion Confirmatory Study－

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A multicenter study was performed to confirm the appropriateness of the dose conversion ratio for switching to HFT-290, which was established based on a new conversion ratio (morphine : fentanyl = 100 : 1). The subjects were patients whose cancer pain was controlled by morphine preparations or oxycodone hydrochloride hydrate sustained-release tablets. HFT-290 was applied at the same dose once daily for 7 days, and the difference in the severity of pain at rest (change of the VAS pain score) between the time of enrollment and final removal of HFT-290 (discontinuation) was evaluated as the primary end-point.

Of 68 patients who consented to participation in this study, 66 were enrolled. Among them, 65 patients (morphine group : 29, oxycodone group : 36) and 42 patients (morphine group : 19, oxycodone group : 23) were classified as the FAS and PPS, respectively.

In the FAS, the 95% confidence interval for the percent change of the VAS pain score was −3.4 to 4.6 mm. Because the upper and lower limit values of the 95% confidence interval were both 15 mm or less, the appropriateness of the dose conversion ratio was confirmed. Similar results were obtained in the groups receiving morphine or oxycodone as the prior opioid analgesics. The VAS pain score remained stable before and after switching in both groups, i.e., satisfactory pain control was maintained. The dose conversion ratio for HFT-290 was considered to be appropriate from both morphine preparations and oxycodone hydrochloride hydrate sustained-release tablets.

Adverse drug reactions caused by HFT-290 similar to those due to conventional transdermal preparations of fentanyl, and none of them had any clinical implications.

These results suggest that the new conversion ratio for switching to HFT-290 from morphine preparations or oxycodone hydrochloride hydrate sustained-release tablets to HFT-290 is appropriate, so that pain will also be controlled satisfactorily after switching.

Key words : HFT-290 ; fentanyl citrate ; cancer pain ; conversion ratio ; transdermal patch

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はじめに

現在，経口モルヒネの代替となる強オピオイド鎮痛薬として，本邦においてもフェンタニル経皮吸収型製剤やオキシコドン塩酸塩水和物徐放錠が販売され，WHO 方式がん疼痛治療法[1]に整合したオピオイドローテーションが可能となった。

しかしながら，従来のフェンタニル経皮吸収型製剤は3日に1回貼付の用法であるため，患者によっては貼付後1～3日にかけて血中フェンタニル濃度が低下し，鎮痛効果が3日間持続しない可能性が示唆されている[2]。また，従来のフェンタニル経皮吸収型製剤で用いられているオピオイド鎮痛薬からの切り替え換算比（モルヒネ：フェンタニル＝150：1）では十分な鎮痛効果が得られない可能性が示唆されている[3)~5)]。

HFT-290（商品名フェントス®テープ）は，1枚あたりフェンタニルクエン酸塩として1，2，4，6および8 mg を含有する製剤（それぞれ5，10，20，30および40cm^2）5規格を有する初めての1日1回貼付のがん疼痛治療剤である。HFT-290は1日1回貼付であることから，血中濃度の低下による鎮痛効果減弱の可能性が低く，24時間ごとに痛みの評価と副作用の有無を確認し，時刻を決めて規則正しく投与するというオピオイド鎮痛薬服用の基本原則（by the clock）を守りやすいといった臨床上のメリットを有する[6]。

今回我々は，モルヒネ製剤またはオキシコドン塩酸塩水和物徐放錠を使用しているがん疼痛患者を対象に，新しい換算比（モルヒネ：フェンタニル＝100：1）に基づいて設定されたHFT-290の切り替え用量の妥当性を検討したので報告する。

本試験は，国内29施設の多施設共同研究として2006年1月から8月まで実施された。なお，本試験は厚生労働省令第28号（平成9年3月27日付）「医薬品の臨床試験の実施の基準に関する省令（GCP）」，その他の関連通知を遵守し，各医療機関の治験審査委員会（IRB）の承認を得た後に実施した。また，本試験への参加について，患者本人の自由意思による同意を文書により得た。

I　対象および方法

1．対象

1）選択基準

対象は既に告知されている20歳以上のがん疼痛患者で，同意取得時，HFT-290貼付開始前日および当日（症例登録時）に以下の項目を満たす患者とした。

(1) モルヒネ製剤ではモルヒネ経口投与量換算で89mg/day以下，またはオキシコドン塩酸塩水和物徐放錠では59mg/day以下であり，用量が一定の患者
(2) レスキュードーズ回数が1日2回以下の患者
(3) 24時間の安静時の平均的な痛みがVisual Analogue Scale（疼痛VAS）で35mm未満の患者

2）除外基準

以下の項目に該当する患者は対象から除外した。

(1) 試験開始時の臨床検査およびバイタルサインの結果が以下に該当する患者
　AST（GOT）：基準値上限の5倍を超える，ALT（GPT）：基準値上限の5倍を超える，血清クレアチニン：基準値上限の3倍を超える，体温：35℃以下または40℃以上
(2) 貼付部位の皮膚に異常（湿疹・皮膚炎，色素異常等の皮膚疾患，術後の創傷等）のある患者
(3) 重篤な心・肝・腎機能障害，重篤な呼吸障害，重篤な呼吸抑制，その他重篤な合併症のある患者
(4) 喘息，呼吸機能障害（慢性肺疾患等）のある患者
(5) 徐脈性不整脈のある患者
(6) 脳に器質的障害（脳腫瘍等）のある患者で，頭蓋内圧の亢進，意識障害・昏睡，呼吸障害のうち，1つ以上の所見・症状を有する患者
(7) 痙攣状態にある患者，痙攣発作の既往を有する患者
(8) 急性アルコール中毒の患者
(9) 出血性大腸炎の患者
(10) 細菌性下痢のある患者
(11) ショック状態にある患者
(12) 代謝性アシドーシスのある患者
(13) 甲状腺機能低下症の患者

⑭ 副腎皮質機能低下症の患者
⑮ Performance status（PS）がGrade 4の患者
⑯ フェンタニル製剤，あへんアルカロイド系麻薬に過敏症のある患者
⑰ 薬物依存の既往を有する患者
⑱ HFT-290貼付開始前7日間に以下の治療を行った患者
　麻薬拮抗性鎮痛薬または麻薬拮抗薬の投与，化学療法の開始または途中休止，放射線療法，疼痛評価に影響を及ぼすと考えられる手術，神経ブロック等の実施
⑲ 抗ウイルス化学療法剤またはHIVプロテアーゼ阻害剤が投与されている患者
⑳ 妊婦，産婦，授乳婦，妊娠している可能性のある患者またはHFT-290貼付期間に妊娠を希望する患者
㉑ 同意取得前4週間に他の治験薬が投与された患者
㉒ その他，医師が対象として不適当と判断した患者

2．投与方法

1）HFT-290の貼付方法

1枚中にフェンタニルクエン酸塩を1 mgまたは2 mg含有するHFT-290を用いた。

HFT-290貼付開始前に使用していたモルヒネ製剤またはオキシコドン塩酸塩水和物徐放錠（先行オピオイド鎮痛薬）の用量に基づき，**表1**の切り替え換算表に従い，HFT-290 1 mg製剤または2 mg製剤の24時間貼付に切り替え，用量を変更せずに1日1回7日間貼付した。貼付部位は原則胸部とし，連続して同一箇所に貼付しないこととした。なお，患者ごとにあらかじめ貼付時刻を定め，正確に24時間貼付した。

HFT-290最終剥離後，再びHFT-290貼付開始前と同一成分および用量のオピオイド鎮痛薬に切り替えた。

2）救済措置（レスキュードーズ）

レスキュードーズには，速効性のモルヒネ塩酸塩製剤を使用した。

3．併用薬剤および併用療法

1）鎮痛薬

オピオイド鎮痛薬（麻薬拮抗性鎮痛薬を含む）および麻薬拮抗薬の併用を禁止した。ただし，レスキュードーズは前述のとおりとした。

HFT-290貼付開始前から継続使用している非オピオイド鎮痛薬，鎮痛を目的とした鎮痛補助薬については，用法用量を変更せずに継続することとした。

表1　モルヒネ製剤またはオキシコドン塩酸塩水和物徐放錠からHFT-290への切り替え換算表

モルヒネ製剤（mg/day）	経口投与	≦29	HFT-290 1 mg製剤	0.3mg/day*
	坐剤	≦10		
	注射（静脈内投与）	≦9		
	経口投与	30～89	HFT-290 2 mg製剤	0.6mg/day*
	坐剤	20～40		
	注射（静脈内投与）	10～29		
オキシコドン塩酸塩水和物徐放錠（mg/day）	経口投与	≦19	HFT-290 1 mg製剤	0.3mg/day*
	経口投与	20～59	HFT-290 2 mg製剤	0.6mg/day*

*定常状態における推定平均吸収量（フェンタニルとして）

2）原疾患および合併症に対する治療

化学療法の開始，途中休止を禁止した。HFT-290貼付開始前から継続使用している原疾患および合併症等に対する治療については，用法用量を変更せずに継続することとした。また，有害事象に対する治療については可とした。

3）併用療法

放射線療法，疼痛評価に影響を及ぼすと考えられる手術，神経ブロック等の治療を禁止した。

4）その他

抗ウイルス化学療法剤，HIVプロテアーゼ阻害剤および他の治験薬の併用を禁止した。

4．観察，検査，評価項目

表2に主な観察，検査，評価項目のスケジュールを示した。

1）患者背景

性別，生年月日，入院・外来の区分，身長，体重，PS，原疾患名，原発部位，転移部位，疼痛部位，合併症，既往歴，HFT-290貼付開始前7日間の前治療を調査した。

2）疼痛VAS

「全く痛みはない（0 mm)」から「これ以上の痛みは考えられない，またはあなたが想像できる最高の痛み（100mm)」までの100mm VASを用いた。

HFT-290貼付開始前，毎日のHFT-290貼り替え時，HFT-290最終剥離時（中止時）および後観察期に，患者が直前24時間を振り返ったときの安静時の平均的な痛みの強さを100mm VASを用いて評価した。

3）レスキュードーズ

レスキュードーズを実施した場合は，投与時刻および投与量を記録した。

4）切り替え改善度

症例登録時と各評価日の疼痛VAS値より，表3の判定基準に従って切り替え改善度を5段階で評価した。「コントロール良好」以上を有効とした。

5）臨床検査

事前検査時およびHFT-290最終剥離時（中止時）に以下の項目を実施した。

(1) 血液学的検査

白血球数，白血球分画（好中球または杆状核球・分葉核球，リンパ球，単球，好酸球，好塩基球)，赤血球数，血色素量，ヘマトクリット値，血小板数

(2) 血液生化学検査

AST（GOT)，ALT（GPT)，γ-GTP，ALP，総ビリルビン，総蛋白，アルブミン，BUN，血清ク

表2　主な観察，検査，評価項目のスケジュール

	事前検査	症例登録	HFT-290貼付期間							後観察期	
Day		0 貼付開始	1	2	3	4	5	6	7 最終剥離†	8～13	14 後観察期終了
同意取得	○										
HFT-290の貼付		○	○	○	○	○	○	○			
患者背景	○										
診察	○	○							○		○
身長，体重	○										
PS		○									
心電図	○								○		
バイタルサイン		○							○		
臨床検査	○								○		
患者日誌（疼痛VAS，レスキュードーズ）	○	○	○	○	○	○	○	○	○	○	○
切り替え改善度			○	○	○	○	○	○	○		
有害事象		○	○	○	○	○	○	○	○	△*	△*

*重篤な有害事象については，後観察期まで調査する。
†中止時は可能な限り最終剥離時の観察，検査および評価を行う。
PS＝performance status，VAS＝visual analogue scale

表3　切り替え改善度の判定基準*

		各評価時の疼痛 VAS (mm)										
		0～4	5～14	15～24	25～34	35～44	45～54	55～64	65～74	75～84	85～94	95～100
症例登録時の疼痛 VAS (mm)	0～4	2	2	2	3	3	4	5	5	5	5	5
	5～14	1	2	2	2	3	4	5	5	5	5	5
	15～24	1	1	2	2	3	4	5	5	5	5	5
	25～34	1	1	1	2	3	4	5	5	5	5	5

*1：コントロール改善，2：コントロール良好，3：コントロールやや良好，4：コントロール低下，5：コントロール不良
VAS＝visual analogue scale

レアチニン，Na，K，Cl

(3) 尿検査（定性）

蛋白，糖，ウロビリノーゲン

(4) 妊娠検査（HCG）

事前検査時に医師が必要と判断した女性のみ実施した。

6）バイタルサインおよび心電図

事前検査時に心電図（標準12誘導）検査を実施した。症例登録時，HFT-290最終剥離時（中止時）に血圧，脈拍数，体温，呼吸数を測定した。

7）有害事象および副作用

HFT-290貼付期間を通じて有害事象（臨床検査値異常変動を含む）を調査し，重症度（1：軽度，2：中等度，3：高度の3段階），重篤度およびHFT-290との因果関係（1：あり，2：たぶんあり，3：たぶんなし，4：なしの4段階）を判定した。重篤な有害事象については，後観察期終了時まで調査した。有害事象のうち，HFT-290との因果関係が否定できないものを副作用とした。なお，重症度の定義は以下のとおりとした。

軽　度：例えば特別な治療を必要とせず，試験の継続は可能な程度

中等度：例えば治療を必要とするが，試験の継続は可能な程度

高　度：例えば試験の中止が必要と考えられる程度

5．中止基準

次のいずれかに該当する場合，試験を中止し，中止時に可能な限り必要な観察，検査および評価を行うとともに，中止日および中止理由を調査した。

1）患者が試験への参加取り止めを希望した場合

2）HFT-290貼付期間に40.0℃以上の発熱が認められた場合

3）HFT-290貼付期間に35.0℃以下の低体温が認められた場合

4）有害事象の発現により，医師がHFT-290貼付の継続を不適当と判断した場合

5）疼痛コントロールが不良となり，医師がHFT-290の増量を必要と判断した場合

6）併用禁止薬を使用した場合，併用禁止療法を施行した場合

7）その他，医師が試験の継続を不適当と判断した場合

6．症例の取扱い

問題症例について，医学専門家および治験調整委員等による症例検討会で検討し，解析上の取扱いを決定した。

7．統計解析

切り替え前の先行オピオイド鎮痛薬別に群を設定し，解析した。モルヒネ製剤からHFT-290に切り替えた患者を「モルヒネ群」，オキシコドン塩酸塩水和物徐放錠からHFT-290に切り替えた患者を「オキシコドン群」とした。

有効性の主要評価項目は，切り替え前後の疼痛VAS値変化量とした。症例登録時（HFT-290貼付開始前）から最終剥離時（中止時）の疼痛VAS値変化量について，平均値の95％信頼区間の上限および下限の絶対値がいずれも15mm以下のとき，同等性が検証されたものとした。

最大の有効性解析対象集団（Full Analysis Set：FAS）を有効性の主解析とした。ただし，主要評価項目については，治験実施計画書に適合した対象集団（Per Protocol Set：PPS）を対象とした解析も実施した。また，治験薬未投与例，安全性に関するデータがない症例およびGCP違反例を除外した集団を安全性解析対象集団とした。

有害事象の事象名はMedDRA/J version 9.1に従って読み替えを行い，器官別大分類（System Organ

Class：SOC）および基本語（Preferred Term：PT）ごとに集計した。

8．目標症例数およびその設定根拠

本試験に先立ち実施した第Ⅱ相試験であるモルヒネ製剤からの切り替え貼付試験における，HFT-290貼付開始前から開始後7日の疼痛VAS値変化量の平均値および標準偏差より，症例数設定に用いるパラメータを以下のとおり設定した。このとき，検出力80％を確保するために必要な症例数は$|\delta|$=5 mmのときに最大で，45例であった。

・母平均：$-5\,\text{mm} \leqq \delta \leqq 5\,\text{mm}$

・同等性マージン：$\Delta = 15\text{mm}$

・標準偏差：$\sigma = 20\text{mm}$

HFT-290の用量別（1 mg/dayまたは2 mg/day）に10例以上を目標とし，かつ先行オピオイド鎮痛薬別に評価可能な症例数を確保し，各々について症例をできるだけ均等に集積するために目標症例数を60例とした。

Ⅱ 結　　果

1．解析対象

患者の内訳を図1に示した。68例の患者より同意を取得し，66例（モルヒネ群30例，オキシコドン群36例）の患者が登録された。登録後，1例がHFT-290貼付前に中止したため，HFT-290を貼付した患者は65例（モルヒネ群29例，オキシコドン群36例）であった。65例中，6例が中止し，59例（モルヒネ群25例，オキシコドン群34例）が試験を完了した。

登録された患者66例のうち，安全性解析対象集団は65例（モルヒネ群29例，オキシコドン群36例），FASは65例（モルヒネ群29例，オキシコドン群36例），PPSは42例（モルヒネ群19例，オキシコドン群23例）であった。

2．患者背景

FASの患者背景を表4に示した。PSはGrade 1が最も多かった。症例登録時の平均疼痛VAS値は

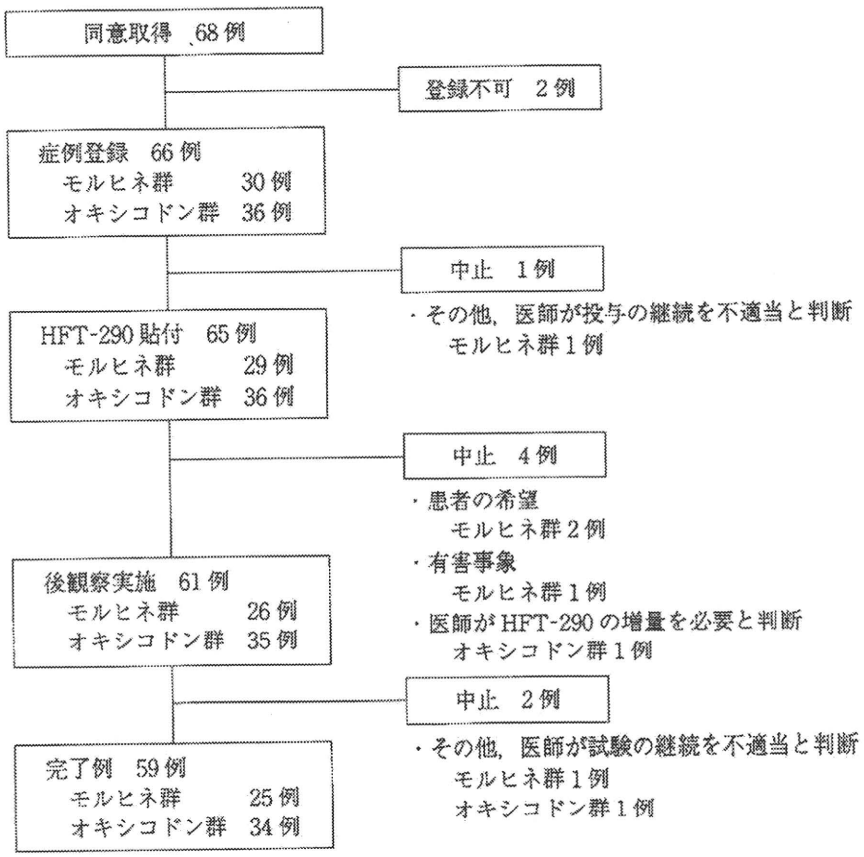

図1　患者の内訳

表4　患者背景（FAS）

項目	分類	全体	モルヒネ群	オキシコドン群
解析対象例数		65	29	36
性別	男	40（61.5%）	13（44.8%）	27（75.0%）
	女	25（38.5%）	16（55.2%）	9（25.0%）
年齢（歳）	平均値	65.4	64.4	66.3
	標準偏差	9.9	11.4	8.6
	中央値	67.0	65.0	67.0
	最小値～最大値	39～83	39～82	49～83
身長（cm）	平均値	159.0	157.0	160.6
	標準偏差	8.7	9.7	7.5
	中央値	160.0	158.0	161.0
	最小値～最大値	134～178	134～172	148～178
体重（kg）	平均値	51.6	48.4	54.2
	標準偏差	9.7	8.6	9.9
	中央値	51.0	49.0	54.0
	最小値～最大値	31～79	31～70	35～79
PS	Grade0	18（27.7%）	11（37.9%）	7（19.4%）
	Grade1	34（52.3%）	13（44.8%）	21（58.3%）
	Grade2	10（15.4%）	4（13.8%）	6（16.7%）
	Grade3	3（ 4.6%）	1（ 3.4%）	2（ 5.6%）
疼痛VAS値（症例登録時）（mm）	平均値	13.1	13.9	12.5
	標準偏差	9.9	11.1	8.8
	中央値	11.0	11.0	11.5
	最小値～最大値	0～33	0～32	0～33
疼痛部位*	頭部	6	4	2
	上肢・肩部	8	2	6
	前胸部	8	3	5
	腹部	30	16	14
	背部	17	10	7
	腰部	9	2	7
	臀部	3	0	3
	下肢部	10	5	5
	その他	4	2	2
先行オピオイド鎮痛薬*	塩酸モルヒネ（静注）	3	3	0
	アンペック®（坐剤）	3	3	0
	MSコンチン®内服	12	12	0
	カディアン®内服	9	9	0
	オキシコンチン®内服	36	0	36
	その他	4	3	1

*重複集計
PS＝performance status，VAS＝visual analogue scale

13.1mm（モルヒネ群13.9mm，オキシコドン群12.5mm）であった。疼痛部位は，腹部が最も多く，次いで背部であった。

また，HFT-290の用量の内訳は，1 mg/dayが30例（モルヒネ群13例，オキシコドン群17例），2 mg/dayが35例（モルヒネ群16例，オキシコドン群19例）であった。

3．有効性

1）主要評価項目（切り替え前後の疼痛VAS値変化量）

症例登録時からHFT-290最終剥離時（中止時）の疼痛VAS値変化量を表5に示した。FASにおいて，疼痛VAS値変化量（平均値±標準偏差，以下同様）は0.6±16.1mm，95％信頼区間は−3.4～4.6mmであり，95％信頼区間の上限および下限の

表5　症例登録時からHFT-290最終剥離時（中止時）の疼痛VAS値変化量（FAS）

		平均値	標準偏差	中央値	最小値～最大値	95%信頼区間
全体（n＝65）	症例登録時	13.1	9.9	11.0	0～33	－
	HFT-290最終剥離時（中止時）	13.8	16.4	8.0	0～100	－
	疼痛VAS値変化量	0.6	16.1	－1.0	－21～99	－3.4～4.6
モルヒネ群（n＝29）	症例登録時	13.9	11.1	11.0	0～32	－
	HFT-290最終剥離時（中止時）	18.8	21.7	13.0	0～100	－
	疼痛VAS値変化量	4.9	22.4	0.0	－17～99	－3.6～13.4
オキシコドン群（n＝36）	症例登録時	12.5	8.8	11.5	0～33	－
	HFT-290最終剥離時（中止時）	9.7	8.7	8.0	0～31	－
	疼痛VAS値変化量	－2.8	7.0	－2.0	－21～15	－5.2～－0.4

VAS＝visual analogue scale　　疼痛VAS値：mm

表6　有効率（FAS）

	有効例数	有効率（%）	95%信頼区間（%）
全体　（n＝65）	56	86.2	75.3～93.5
モルヒネ群　（n＝29）	24	82.8	64.2～94.2
オキシコドン群（n＝36）	32	88.9	73.9～96.9

絶対値が15mm以下であったことから，用量換算の妥当性は検証された。また，PPSの疼痛VAS値変化量は－1.6±10.4mm，95%信頼区間は－4.8～1.6mmであり，結果の頑健性が確認された。

先行オピオイド鎮痛薬別では，切り替え前後の疼痛VAS値変化量の95%信頼区間は，モルヒネ群－3.6～13.4mm，オキシコドン群－5.2～－0.4mmであった。PPSの先行オピオイド鎮痛薬別の結果も同様であった。

2）切り替え改善度

全体，モルヒネ群，オキシコドン群の切り替え改善度について，HFT-290最終剥離時（中止時）の有効率を表6に示した。全体の有効率は86.2%（56/65例）と良好な結果であった。先行オピオイド鎮痛薬別では，モルヒネ群82.8%（24/29例），オキシコドン群88.9%（32/36例）と各群とも良好な有効率であった。

3）疼痛VAS，レスキュードーズ回数

FASでの各評価日の疼痛VAS値およびレスキュードーズ回数の推移を図2に示した。

疼痛VAS値（平均値±標準偏差）は，症例登録時に13.1±9.9mmを示し，HFT-290貼付開始後1～7日にかけて12.3±11.8～14.4±13.0mmの範囲を推移した。後観察期終了時の疼痛VAS値は15.7±16.0mmであった。先行オピオイド鎮痛薬別では，オキシコドン群よりもモルヒネ群の方がやや高い疼痛VAS値を示したが，切り替え前後の疼痛VAS値の推移は各群ともほぼ一定であり，良好な疼痛管理が維持された。

平均レスキュードーズ回数は，モルヒネ群で切り替え直後にやや増加する傾向がみられたが，その後はほぼ一定に推移し，症例登録時からHFT-290貼付開始後7日まで1回/day未満であった。

4．安全性評価

1）有害事象および副作用

有害事象および副作用発現率を表7に，事象別（SOC，PT別）の副作用を表8に示した。

全体において，有害事象発現率は87.7%（57例）235件，副作用発現率は60.0%（39例）82件であった。貼付部位の副作用は，9.2%（6例）6件であった。先行オピオイド鎮痛薬別では，モルヒネ群の副作用発現率は51.7%（15例）36件，オキシコドン群の副作用発現率は66.7%（24例）46件であった。

発現した副作用の内訳（発現率5%以上）は，便

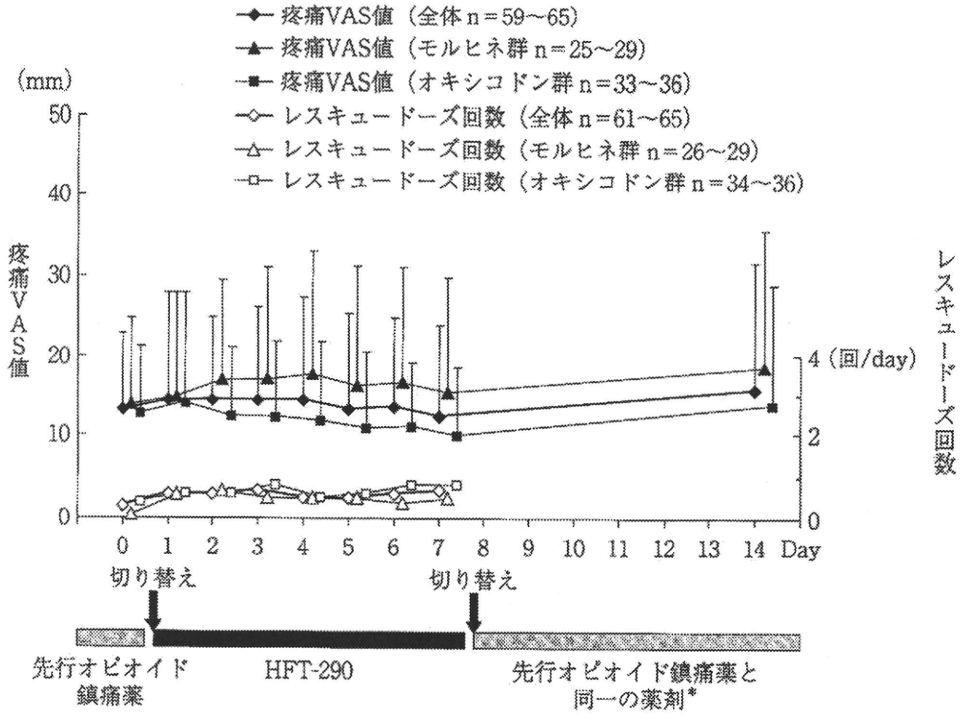

図2　疼痛 VAS 値およびレスキュードーズ回数の推移（FAS）

*先行オピオイド鎮痛薬と同一成分および用量のオピオイド鎮痛薬
VAS＝visual analogue scale

表7　有害事象および副作用発現率（安全性解析対象集団）

		例数	件数	発現率（%）
全体（n＝65）	有害事象	57	235	87.7
	副作用	39	82	60.0
	自覚症状および他覚所見			
	貼付部位	6	6	9.2
	貼付部位以外	31	54	47.7
	臨床検査値異常変動，バイタルサインおよび心電図異常	9	22	13.8
モルヒネ群（n＝29）	副作用	15	36	51.7
	自覚症状および他覚所見			
	貼付部位	1	1	3.4
	貼付部位以外	12	20	41.4
	臨床検査値異常変動，バイタルサインおよび心電図異常	4	15	13.8
オキシコドン群（n＝36）	副作用	24	46	66.7
	自覚症状および他覚所見			
	貼付部位	5	5	13.9
	貼付部位以外	19	34	52.8
	臨床検査値異常変動，バイタルサインおよび心電図異常	5	7	13.9