重要情報
がんに関する相談は相談支援センターへ

がん診療連携拠点病院の指定を受けた全国377ヵ所の病院には、「相談支援センター」が設置されています。
「患者の権利」を守るために作られた相談支援センターは、それぞれの病院に入院・通院中の患者さんばかりでなく、他の医療機関を受診している患者さんや家族、一般市民からのがんに関する相談や質問にも対応します。その病院で診察を受けていなくても、面談や電話で相談することができます。(病院によっては、「医療相談室」「がん相談支援室」「よろず相談室」「地域医療連携室」など、別の名前で呼ばれていることもあります。)
相談支援センターでは、がんの専門研修を受けたソーシャルワーカー、看護師、カウンセラー、薬剤師、療法士、栄養士などが連携をとり、患者さんのさまざまな悩みの相談を受け付けています。また、医療に関するアドバイスが必要な場合は、主治医とのやりとりの橋渡し役にもなります。
相談支援センターは、がんに関わるあらゆる相談に応じます。面談でも電話相談でもかまいません。悩みや困ったことがあれば、ぜひ利用してください。
たとえば以下のような相談にも、相談支援センターは対応します。

治療上の悩み

・検査にひっかかりました。がんかもしれないと不安です。どこの病院で診察を受けたらいいですか？
・私のがんは、どんながんなのでしょうか？
・診察のときに主治医が言っていた専門用語がわからなくて困っています。
・痛みを緩和する治療をしてもらうには、どうしたらよいのでしょうか？
・薬や治療の内容についてもう少し詳しく教えてほしいのですが。
・主治医がなんとなく怖くて、うまく話ができません。
・セカンド・オピニオンをとるには、どうしたらよいのでしょうか？
・症状の記録ノートをとるようにと言われたのですが、書き方がわかりません。
・在宅ケアを利用したいのですが、どうしたらよいでしょうか？
・知人に勧められた代替療法のサプリメントを飲んでいるのですが、治療に支障はないでしょうか？

心の悩み

・がんになってしまって、「私はこれからどうなるのか」、と不安で眠れません。
・仕事をどうしたらいいか悩んでいます。
・治療が終わったのですが、職場復帰について悩んでいます。会社の人にはどう告げたらよいのでしょう？
・小さな子供がいるのですが、がんのことをどう伝えたらよいのでしょうか？
・もしものときのため、遺言の準備や財産整理についてのアドバイスがほしいのですが。

がん治療・療養にかかるお金の悩み

・高額療養制度、介護制度などを利用する方法や手続きについて教えて下さい。
・民間の保険に入っていますが、給付金を受け取るにはどうしたらよいのでしょうか？

家族の悩み

・配偶者ががんになって、心を閉ざしてしまいました。どう対応したらよいのでしょうか？
・身近な家族ががんになったことで、気分が落ち込んでしかたがありません。

あなたの地域の相談支援センター

がんに関するご質問やご相談はお近くの「がん診療連携拠点病院」の相談支援センターで受けつけています。お近くの拠点病院をさがしたいときには、がん情報サービス　http://ganjoho.jp/ またはがん情報サービス　携帯版　http://ganjoho.jp/mn をご参照ください。右のQRコードをお使いいただけます。

知っておくと役に立つインターネットサイト

がんの治療や緩和ケアについては、インターネットを使ってさまざまな情報を手に入れることができます。参考になるサイトをご紹介します。

がん情報サービス（国立がん研究センター）

がんの患者さんにとって必要な情報を網羅。
様々な種類のがんや緩和ケアについて解説した
「がんの冊子シリーズ」や「患者必携」などの冊子もダウンロード可能。
http://ganjoho.jp/

がんの痛みネット

がんの痛みとその治療法や緩和ケアについて、くわしい情報を掲載。
http://www.itaminai.net/

緩和ケア.net

緩和ケアについて、やさしい解説を掲載。
http://www.kanwacare.net/

がん情報サイト

米国国立がん研究所が提供しているがん情報サイトPDQ®の日本語版。
http://cancerinfo.tri-kobe.org/

日本ホスピス緩和ケア協会

緩和ケアの普及と発展を目指す同協会のホームページ。
http://www.hpcj.org/

日本ホスピス・緩和ケア研究振興財団

ホスピス・緩和ケアについての研究や調査などの情報を掲載。
http://www.hospat.org/

推薦図書

『患者必携　がんになったら手にとるガイド』ほか

国立がん研究センターがん対策情報センター発行

がんの療養に関するさまざまな情報をまとめた「がんになったら手にとるガイド」のほか、療養中の患者さんが病状を記録し、知りたいことなどを書きとめて整理できる「わたしの療養手帳」などの冊子があり、全国のがん診療連携拠点病院のがん相談支援センターで閲覧できる。また、これらの冊子はすべて「がん情報サービス」のサイト（38ページ）からダウンロードすることもできる。

『あなたの家にかえろう』

「おかえりなさい」プロジェクト事務局（桜井隆）著

在宅ホスピスケアについての基礎的な情報がまとめられており、サービスの探し方などについても解説している。著者のホームページもある。
http://www.reference.co.jp/sakurai/

『こころに寄り添う緩和ケア―病いと向き合う「いのち」の時間』

井西鷹子著、新曜社

病と向き合う患者のために取り組むチーム医療の実践を通して、「終末期」医療の可能性をさぐる。

『がん患者さんの心と体の悩み解決ガイド』

日経メディカル編集、日経BP社

がん患者の抱える悩みや疑問に医師、看護師、ソーシャルワーカーなど、複数の専門家がそれぞれの立場から回答。

『家で看取るということ』

川越厚　川越博美著、講談社

在宅ホスピスケアの現場に携わる著者の視点から、患者さんが自分らしく家で過ごす方法、自宅でのケアの方法などをまとめている。

『がんの痛み対策と緩和ケア』

向山雄人著、主婦の友社

がんの痛みやがんに伴う諸症状、精神的な苦痛などのコントロールについて説明。

『QOLの向上をめざして―がん疼痛緩和ケアQ&A』

加賀谷肇　的場元弘　田中昌代著、株式会社じほう

がんの緩和ケアチーム医療に従事する医師、薬剤師、看護師などの、医療従事者向けのQ&A集。

『がん　家族はどうしたらよいか』

季羽倭文子著、池田書店

家族ががんになったとき、患者の気持ちを理解するために役立つ情報や、告知についての考え方などを紹介。

『家で生きることの意味』

柳田邦男　川越厚著、青海社

在宅ホスピスを選択した人、その家族、そしてそれを支えた医療者が体験を語る。

『がんのひみつ』

中川恵一著、朝日出版社

がんについての基本的な知識と、がんに対する考え方について、放射線科医が書いた入門書。

この冊子づくりは、ひとりのがん患者さんの思いからはじまりました――

この冊子は、発行元であるNHK厚生文化事業団の副理事長をつとめた故・伊東律子さんのご遺族からのご寄付をもとに、国立がん研究センター中央病院の的場元弘先生のご協力を得て作成されました。伊東律子さんは、NHKで長年番組のディレクターやプロデューサーを務めた後、理事として多忙な日々を過ごしていたときにがんに倒れました。その後7年間、2009年12月に他界されるまで、がんという病気と正面から向き合い、自分らしく生きることを心がけ、充実した日々を送るようにつとめられました。

2007年4月に「がん対策基本法」が施行され、日本でも、治療の早い時期からがんの患者さんに緩和ケアを提供するという考え方が打ち出されました。それに伴い、すべての患者さんとご家族が緩和ケアを受けることのできる体制が整備されつつあります。

この小さな冊子が、がん患者さんとご家族の心と体を支える一助になれば、と願っています。

この冊子の作成にあたっては、以下の皆様のご協力を賜りました。
お礼を申し上げます。（敬称略・五十音順）

秋山美紀　（慶應義塾大学総合政策学部准教授）
片山史絵　（あすか山訪問看護ステーション看護師）
加藤雅志　（（独）国立がん研究センター
がん対策情報センターがん医療情報コンテンツ室長、中央病院精神腫瘍科）
佐伯俊成　（広島大学病院総合内科・総合診療科／大学院総合診療医学准教授）
髙橋美賀子（聖路加国際病院看護部がん看護専門看護師）
恒藤暁　（大阪大学大学院医学系研究科緩和医療学教授）
樋口由起子（（独）国立がん研究センター相談支援センター
社会福祉士／精神保健福祉士）
二見典子　（ピースハウス病院副院長・看護部長）
三好綾　（NPO法人がんサポートかごしま理事長）
余宮きのみ（埼玉県立がんセンター緩和ケア科科長兼副部長）
渡邊清高　（（独）国立がん研究センターがん対策情報センターがん情報・統計部
がん医療情報サービス室長）

監修

的場元弘

1959年生まれ。北里大学医学部卒業。オハイオ州立大学病院麻酔科研究員、北里大学医学部麻酔科講師などを経て、現在は、（独）国立がん研究センター中央病院　緩和医療科・精神腫瘍科科長。医学博士。著書に『がん疼痛治療のレシピ』（春秋社）など。

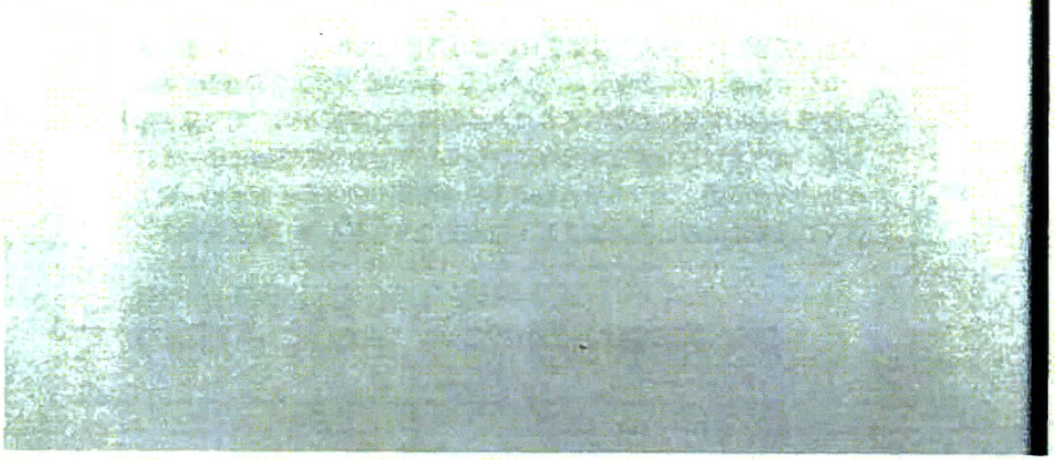
編集・発行

社会福祉法人　NHK厚生文化事業団
1960年（昭和35年）の設立以来NHKの放送と一体になって、さまざまな福祉活動に取り組み、福祉に対する理解の輪を広げています。

主な事業内容
○高齢者福祉、障害者福祉のためのNHKハートフォーラム
○子どもの発達に関する相談会
○障害児・者のキャンプ
○NHK障害福祉賞
○NHKハート展
○福祉番組ビデオの無料貸し出し
○視覚障害者向けのテープライブラリー
○地域の福祉団体を支援する「わかば基金」の贈呈
○福祉機器・福祉車両の贈呈
○NHKボランティアネット
○子どもサポートネット
○NHK歳末・海外たすけあい

〒150-0041 東京都渋谷区神南1-4-1 第七共同ビル
Tel. 03-3476-5955　Fax. 03-3476-5956
ホームページアドレス　http://www.npwo.or.jp

イラスト：金子恵（表紙、p.3-11）　江口修平（p.20-29）
デザイン：fgd 高村雄介
編集協力：川上純子
印　　刷：川崎印刷株式会社
2010年12月10日第1版第1刷発行



発行・社会福祉法人 NHK厚生文化事業団
監修・的場元弘（国立がん研究センター中央病院 緩和医療科・精神腫瘍科科長）

がん疼痛の薬物療法に関するガイドライン

2010年版

編集　特定非営利活動法人 日本緩和医療学会
緩和医療ガイドライン作成委員会

金原出版株式会社

緩和医療ガイドライン作成委員会

委員長	志真　泰夫	筑波メディカルセンター病院緩和医療科
担当委員	戸谷(細矢)美紀	国立がん研究センター中央病院看護部
	的場　元弘	国立がん研究センター中央病院緩和医療科・精神腫瘍科
	森田　達也	聖隷三方原病院緩和支持治療科

がん疼痛ガイドライン作業部会

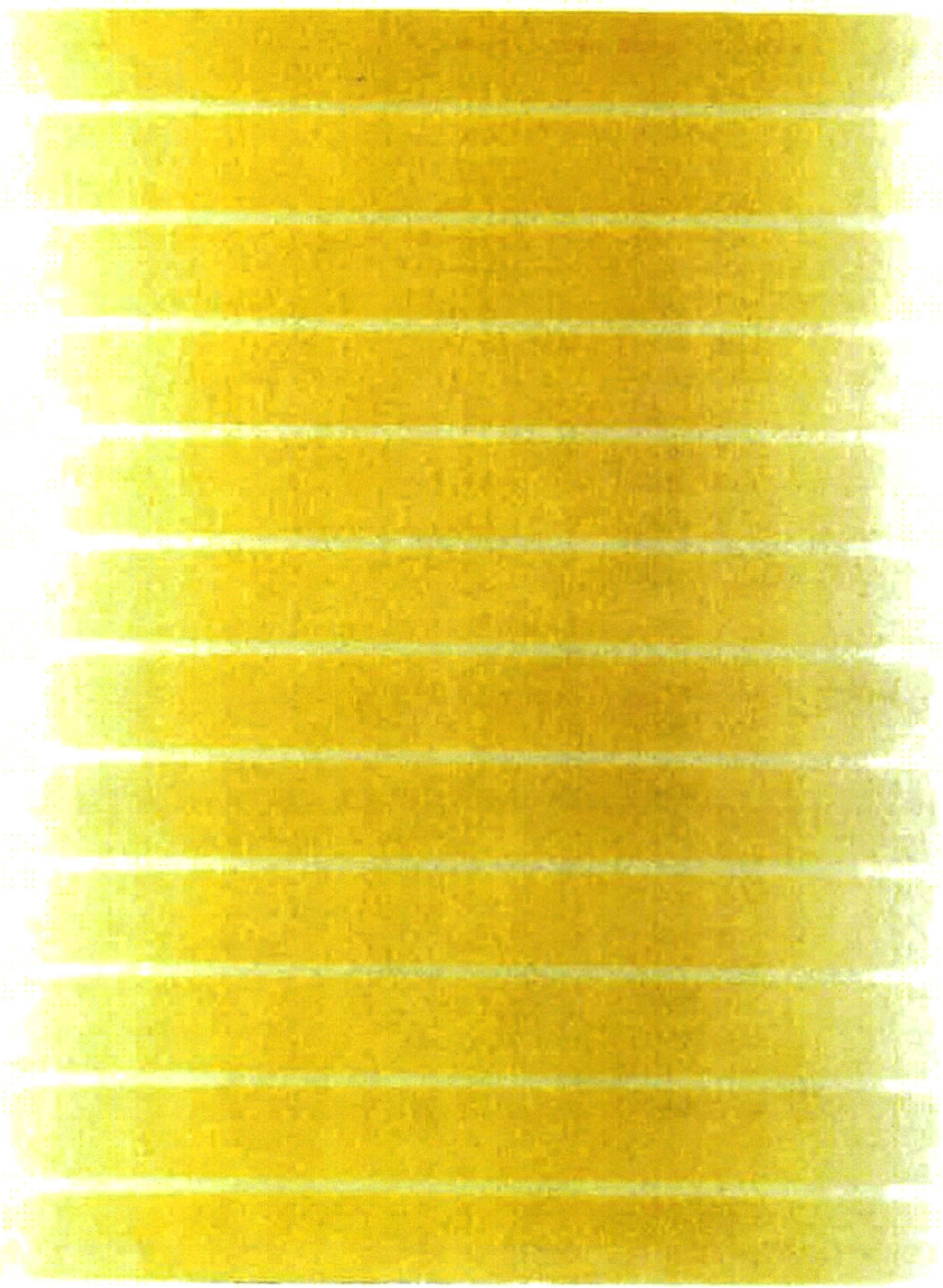
部会長	志真　泰夫	筑波メディカルセンター病院緩和医療科
副部会長	戸谷(細矢)美紀	国立がん研究センター中央病院看護部
	的場　元弘	国立がん研究センター中央病院緩和医療科・精神腫瘍科
	森田　達也	聖隷三方原病院緩和支持治療科
委員	赤木　徹	国立がん研究センター中央病院薬剤部
	荒井　保明	国立がん研究センター中央病院放射線診断科、日本インターベンショナルラジオロジー学会〔外部委員〕
	新幡　智子	慶應義塾大学看護医療学部
	有賀　悦子	帝京大学医学部内科学講座緩和医療科、帝京がんセンター／医療情報システム研究センター
	池永　昌之	淀川キリスト教病院ホスピス
	井沢　知子	京都大学医学部附属病院看護部
	伊勢　雄也	日本医科大学付属病院薬剤部
	井関　雅子	順天堂大学医学部麻酔科・ペインクリニック
	伊東　俊雅	東京女子医科大学病院薬剤部
	射場　典子	NPO法人健康と病いの語りディペックス・ジャパン
	今井　堅吾	淀川キリスト教病院ホスピス
	上園　保仁	国立がん研究センター研究所がん患者病態生理研究部
	上田　敬子	恵佑会札幌病院緩和ケア科
	梅田　恵	株式会社緩和ケアパートナーズ
	大坂　巌	静岡県立静岡がんセンター緩和医療科
	大澤　匡弘	星薬科大学薬物治療学教室
	大畑　美里	聖路加国際病院看護部
	小笠原利枝	横浜市立みなと赤十字病院看護部
	岡本　禎晃	大阪大学大学院薬学研究科実践薬学教育研究センター病院薬学教育研究部
	奥津　輝男	静岡県立静岡がんセンター緩和医療科
	奥出有香子	順天堂大学医学部附属順天堂医院看護部
	加賀谷　肇	済生会横浜市南部病院薬剤部
	風間　郁子	国際医療福祉大学三田病院看護部
	片山　志郎	日本医科大学付属病院薬剤部
	加藤　恵	武蔵野赤十字病院看護部
	川地香奈子	癌研究会有明病院看護部
	川村三希子	北海道医療大学看護福祉学部

木下　寛也	国立がん研究センター東病院緩和医療科・精神腫瘍科
葛巻　直子	星薬科大学薬品毒性学教室
工藤　尚子	国立がん研究センター研究所
国分　秀也	北里大学病院薬剤部
小島　圭子	東京慈恵会医科大学附属病院麻酔科
小原　弘之	県立広島病院緩和ケア科
小宮　幸子	横浜市立大学附属病院薬剤部
小山　弘	国立病院機構京都医療センター教育研修部長〔外部委員〕
小山富美子	近畿大学医学部附属病院がんセンター看護部
境　徹也	長崎大学医学部麻酔学教室
坂元　敦子	杏林大学医学部付属病院看護部
坂本　雅樹	名古屋市立大学病院緩和ケア部
佐々木聡美	みどり内科クリニック
佐野　元彦	埼玉医科大学総合医療センター薬剤部
塩川　満	聖路加国際病院薬剤部
四方　哲	蘇生会総合病院外科〔外部委員〕
宍戸　英樹	宍戸内科医院
篠　道弘	静岡県立静岡がんセンター薬剤部
篠原　明子	帝京大学医学部附属病院緩和医療科
清水わか子	君津中央病院放射線治療科、日本放射線腫瘍学会
白髭　豊	白髭内科医院
新貝夫弥子	愛知県がんセンター中央病院看護部
新城　拓也	社会保険神戸中央病院緩和ケア病棟
須賀　昭彦	静岡済生会総合病院緩和医療科
鈴木　勉	星薬科大学薬品毒性学教室
高瀬　久光	福岡大学病院薬剤部
高田　慎也	国立病院機構北海道がんセンター薬剤科
高田　正史	長崎大学病院麻酔科
瀧川千鶴子	KKR札幌医療センター緩和ケア科
田口　賀子	大阪府立成人病センター看護部
田中　桂子	がん・感染症センター都立駒込病院緩和ケア科
長　美鈴	聖路加国際病院緩和ケア科
敦賀　健吉	北海道大学医学研究科麻酔・周術期医学分野
冨安　志郎	長崎市立市民病院麻酔科・緩和ケアチーム
中川　貴之	京都大学薬学研究科生体機能解析学分野
中西　真理	在宅看護研究センターLLP日本在宅看護システム
成田　年	星薬科大学薬品毒性学教室
西岡　弘晶	名古屋記念病院総合内科
能勢　誠一	長崎大学病院薬剤部
浜野　淳	大和クリニック
林　章敏	聖路加国際病院緩和ケア科

	林　ゑり子	藤沢湘南台病院看護部
	久永　貴之	筑波メディカルセンター病院緩和医療科
	久原　　幸	手稲渓仁会病院がん治療管理センター緩和ケア室・緩和ケアチーム
	尾藤　誠司	NHO東京医療センター教育研修部/臨床疫学研究室〔外部委員〕
	廣岡　佳代	聖路加看護大学看護実践開発研究センター
	府川美沙子	北里大学病院薬剤部
	北條美能留	長崎大学病院麻酔科・緩和ケアチーム
	細川　豊史	京都府立医科大学麻酔科
	細谷　　治	城西大学薬学部薬剤学講座
	本田　晶子	聖路加看護大学看護実践開発研究センター
	前堀　直美	株式会社レーベンプラン レモン薬局三方原店
	松坂　　俊	手稲渓仁会病院総合内科/感染症科・緩和ケアチーム
	松田　陽一	大阪大学大学院医学系研究科麻酔・集中治療医学講座
	松本　直子	聖路加看護大学図書館
	松本　禎久	国立がん研究センター東病院緩和医療科・精神腫瘍科
	三浦　里織	慶應義塾大学病院看護部
	村上　敏史	国立がん研究センター中央病院緩和医療科・精神腫瘍科
	村田　寛明	長崎大学医学部麻酔学教室
	森脇　俊和	筑波大学大学院消化器内科〔外部委員〕
	八戸　すず	順天堂大学がん治療センター緩和ケアチーム
	山口　敬介	順天堂大学医学部麻酔科ペインクリニック講座
	山口　　崇	筑波メディカルセンター病院緩和医療科
	山本　　亮	佐久総合病院総合診療科・緩和ケアチーム
	温泉川真由	国立がん研究センター研究所腫瘍ゲノム解析・情報研究部
	余宮きのみ	埼玉県立がんセンター緩和ケア科
	龍　　恵美	長崎大学病院薬剤部・緩和ケアチーム
	渡邊　紘章	静岡県立静岡がんセンター緩和医療科
	渡邊　眞理	神奈川県立がんセンター地域医療連携室
評価委員	飯野　京子	国立看護大学校成人看護学
	加藤　裕久	昭和大学薬学部医薬品情報学教室〔外部委員〕
	川越　正平	あおぞら診療所
	木澤　義之	筑波大学大学院人間総合科学研究科
	下山　直人	国立がん研究センター東病院緩和医療科・精神腫瘍科
	茶谷　正史	大阪労災病院放射線科〔外部委員〕
	恒藤　　暁	大阪大学大学院医学系研究科緩和医療学
	中島　康雄	聖マリアンナ医科大学放射線医学教室〔外部委員〕
	中山　健夫	京都大学健康情報学〔外部委員〕
	奈良林　至	埼玉医科大学国際医療センター包括的がんセンター緩和医療科
	向山　雄人	癌研有明病院緩和ケア科
	村川　和重	兵庫医科大学疼痛制御科学・ペインクリニック部

ISBN978-4-307-10149-3
C3047 ¥2800E

定価(本体2,800円+税)



SYNAPSE 65:668–676 (2011)

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

YOSHINORI TAKEMURA,[1,2] AKIRA YAMASHITA,[1] HIROSHI HORIUCHI,[1] MASAHARU FURUYA,[1] MAKOTO YANASE,[1] KEIICHI NIIKURA,[1] SATOSHI IMAI,[1] NOBORU HATAKEYAMA,[2] HIROYUKI KINOSHITA,[3] YOSHI TSUKIYAMA,[4] EMIKO SENBA,[5] MOTOHIRO MATOBA,[6] NAOKO KUZUMAKI,[1] MITSUAKI YAMAZAKI,[2*] TSUTOMU SUZUKI,[1*] AND MINORU NARITA[1,2*]

[1]*Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*

[2]*Department of Anesthesiology, Graduate School of Medical and Pharmaceutical Sciences for Education, Toyama University, 2630 Sugitani, Toyama 930-0194, Japan*

[3]*Department of Anesthesiology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan*

[4]*Division of Palliative Medicine, Wakayama Medical University Hospital, 811-1 Kimiidera, Wakayama 641-0012, Japan*

[5]*Department of Anatomy and Neurobiology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan*

[6]*Division of Palliative Medicine and Psycho-Oncology, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

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.** © 2010 Wiley-Liss, Inc.

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

*Correspondence to: Minoru Narita, Ph.D., Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan. E-mail: narita@hoshi.ac.jp; Tsutomu Suzuki, Ph.D. Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan. E-mail: suzuki@hoshi.ac.jp; or Mitsuaki Yamazaki, M.D., Ph.D., Department of Anesthesiology, Graduate School of Medical and Pharmaceutical Sciences for Education, Toyama University, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: myama@med.u-toyama.ac.jp.

Received 10 October 2010; Accepted 28 November 2010

DOI 10.1002/syn.20898

Published online 15 December 2010 in Wiley Online Library (wileyonlinelibrary.com).

© 2010 WILEY-LISS, INC.

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).

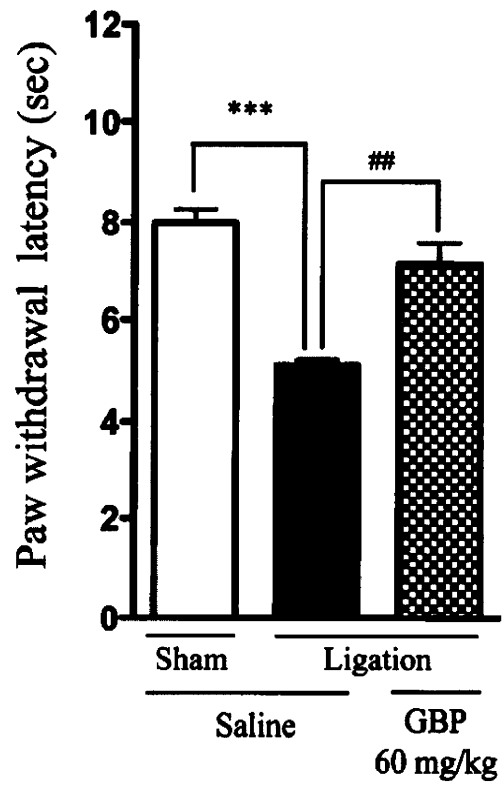


Fig. 1. Effect of gabapentin (GBP) on thermal hyperalgesia induced by nerve ligation in mice. Groups of mice were injected with GBP (60 mg/kg, i.p.) or saline at 7 days after sciatic nerve ligation or sham operation. Thermal hyperalgesia was measured 1 h after a single i.p. injection of GBP or saline 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/

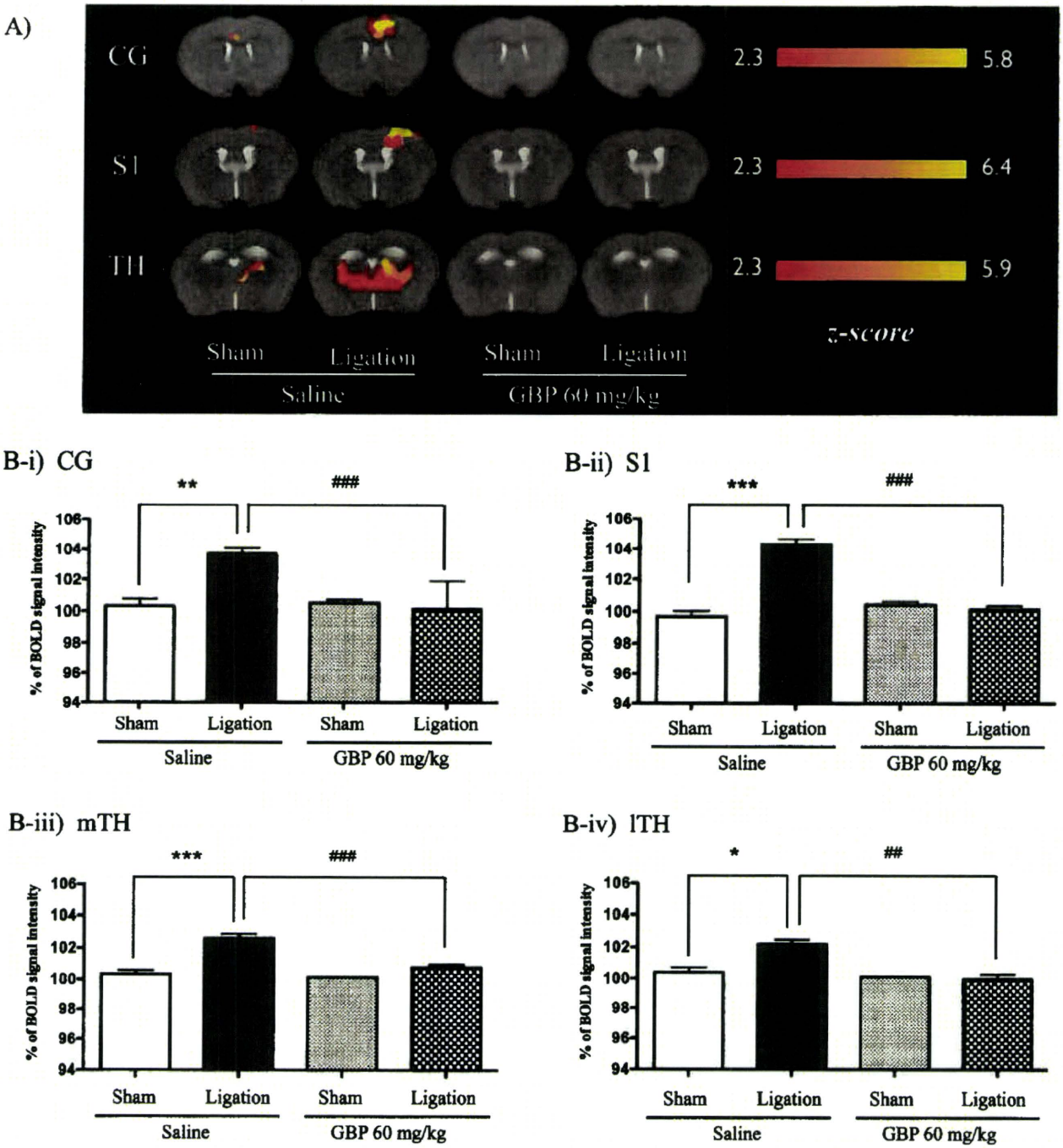


Fig. 2. Effect of gabapentin (GBP) on the increase in BOLD signal intensity induced by sciatic nerve ligation. A: BOLD signal intensity in the cingulate cortex (CG), somatosensory cortex (S1), and thalamic region (TH) was measured 60 min (CG), 80 min (S1), or 100 min (TH), respectively, after a single 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

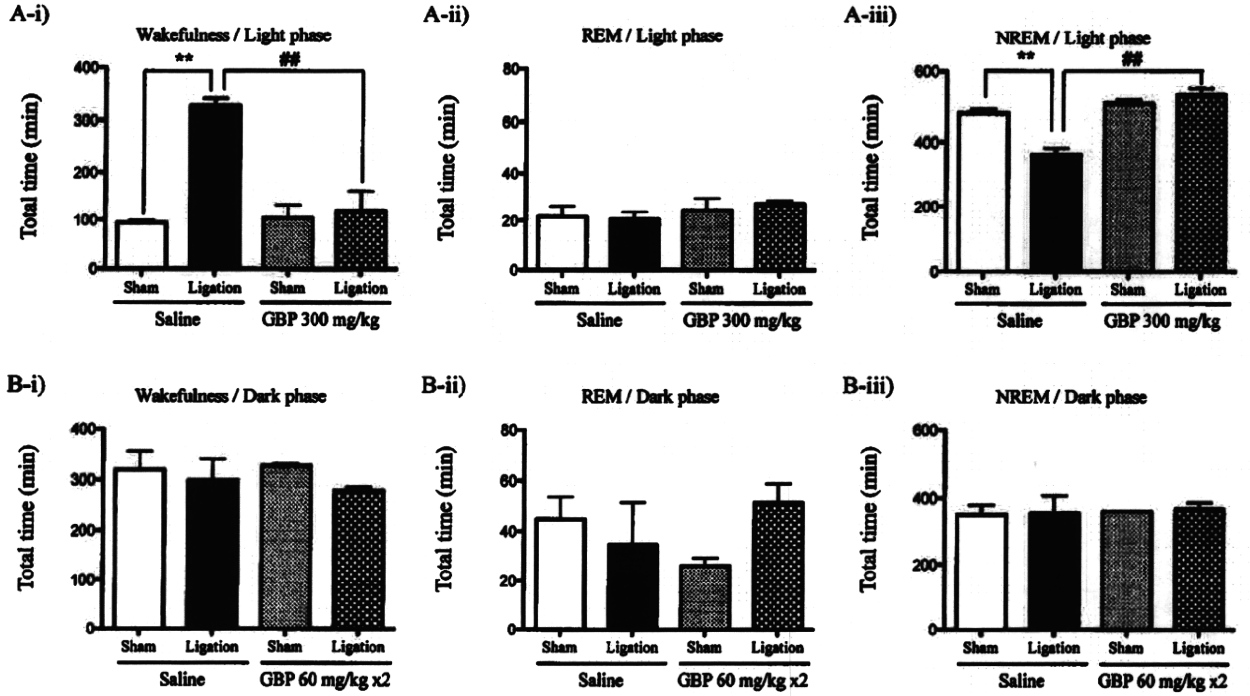


Fig. 3. Changes in sleep vigilance related to hypnotic effects of GBP under a neuropathic pain-like state as determined by EEG/EMG recordings. Sleep-wake states following saline or GBP injection at 7 days after sciatic nerve ligation. Saline or GBP was injected three times at 8:00 p.m. (saline or 60 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.

REFERENCES

Atkinson JH, Ancoli-Israel S, Slater MA, Garfin SR, Gillin JC. 1988. Subjective sleep disturbance in chronic back pain. Clin J Pain 4:225–232.

Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. 2006. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 13:1153–1169.

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. 1998. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. JAMA 280:1831–1836.

Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D. 1999. Human brain activation under controlled thermal stimulation and habituation to noxious heat: An fMRI study. Magn Reson Med 41:1044–1057.

Beiche F, Brune K, Geisslinger G, Goppelt-Struebe M. 1998. Expression of cyclooxygenase isoforms in the rat spinal cord and their regulation during adjuvant-induced arthritis. Inflamm Res 47:482–487.

Borsook D, Moulton EA, Schmidt KF, Becerra LR. 2007. Neuroimaging revolutionizes therapeutic approaches to chronic pain. Mol Pain 3:25.

Chapman V, Suzuki R, Chamarette HL, Rygh LJ, Dickenson AH. 1998. Effects of systemic carbamazepine and gabapentin on spinal neuronal responses in spinal nerve ligated rats. Pain 75:261–272.
Chizh BA, Scheede M, Schlutz H. 2000. Antinociception and (R,S)-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid antagonism by gabapentin in the rat spinal cord in vivo. Naunyn Schmiedebergs Arch Pharmacol 362:197–200.
Coderre TJ, Kumar N, Lefebvre CD, Yu JS. 2007. A comparison of the glutamate release inhibition and anti-allodynic effects of gabapentin, lamotrigine, and riluzole in a model of neuropathic pain. J Neurochem 100:1289–1299.
Couceiro TC, Menezes TC, Valênça MM. 2009. Post-mastectomy pain syndrome: The magnitude of the problem. Rev Bras Anestesiol 59:358–365.
Craig AD. 1996. An ascending general homeostatic afferent pathway originating in lamina I. Prog Brain Res 107:225–242.
Dooley DJ, Taylor CP, Donevan S, Feltner D. 2007. Ca^{2+} channel alpha2delta ligands: Novel modulators of neurotransmission. Trends Pharmacol Sci 28:75–82.
Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. 2000. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Anesth Analg 91:185–191.
Field MJ, Hughes J, Singh L. 2000. Further evidence for the role of the alpha(2)delta submit of voltage dependent calcium channels in models of neuropathic pain. Br J Pharmacol 131:282–286.
Fox A, Gentry C, Patel S, Kesingland A, Bevan S. 2003. Comparative activity of the anti-convulsants oxcarbazepine, carbamazepine, lamotrigine and gabapentin on a model of neuropathic pain in the rat and guinea-pig. Pain 105:355–362.
Galer BS, Gianas A, Jensen MP. 2000a. Painful diabetic polyneuropathy: Epidemiology, pain description, and quality of life. Diabetes Res Clin Pract 47:123–128.
Galer BS, Henderson J, Perander J, Jensen MP. 2000b. Course of symptoms and quality of life measurement in Complex Regional Pain Syndrome: A pilot survey. J Pain Symptom Manage 20:286–292.
Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. 1996. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem 271:5768–5776.
Goppelt-Struebe M, Beiche F. 1997. Cyxlooxygenase-2 in the spinal cord: Localization and regulation after a peripheral inflammatory stimulus. Adv Exp Med Biol 433:213–216.
Governo RJ, Morris PG, Marsden CA, Chapman V. 2008. Gabapentin evoked changes I functional activity in nociceptive regions in the brain of the anaesthetized rat: An fMRI study. Br J Pharmacol 153:1558–1567.
Han ZS, Zhang ET, Craig AD. 1998. Nociceptive and thermoreceptive lamina I neurons are anatomically distinct. Nat Neurosci 1:218–225.
Haythornthwaite JA, Hegel MT, Kerns RD. 1991. Development of a sleep diary for chronic pain patients. J Pain Symptom Manage 6:65–72.
Hazelrigg SR, Cetindag IB, Fullerton J. 2002. Acute and chronic pain syndromes after thoracic surgery. Surg Clin North Am 82:849–865.
Hempenstall K, Nurmikko TJ, Jonhson RW, A'Hern RP, Rice AS. 2005. Anelgesic therapy in postherpetic neuralgia: 1 Quantitative systematic review. PLoS Med 2:e164.
Honey GD, Corlett PR, Absalom AR, Lee M, Pomarol-Clotet E, Murray GK, McKenna PJ, Bullmore ET, Menon DK, Fletcher PC. 2008. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci 28:6295–6303.
Honore P, Luger NM, Sabino MA, Schwei MJ, Rogers SD, Mach DB, O'Keefe PF, Ramnaraine ML, Clohisy DR, Mantyh PW. 2000. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. Nat Med 6:521–528.
Hunter JC, Gogas KR, Hedley LR, Jacobson LO, Kassotakis L, Thompson J, et al. 1997. The effect of novelanti-epileptic drugs in rat experimental models of acute and chronic pain. Eur J Pharmacol 324:153-160.
Hwang JH, Yaksh TL. 1997. Effect of subarachnoid gabapentin on tactile-evoked allodynia in a surgically induced neuropathic pain model in the rat. Reg Anesth 22:249–256.
Iannetti GD, Zambreanu L, Wise RG, Buchanan TJ, Huggins JP, Smart TS, et al. 2005. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci USA 102:18195–18200.
Ji RR, Woolf CJ. 2001. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiol Dis 8:1–10.
Jones AK, Brown WD, Friston KJ, Qi LY, Frackowiak RS. 1991. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc Biol Sci 244:39–44.
Jones DL, Sorkin LS. 1998. Systemic gabapentin and S(+)-3-isobutyl-gamma-aminobutyric acid block secondary hyperalgesia. Brain Res 810:93–99.
Joshi SK, Hernandez G, Mikusa JP, Zhu CZ, Zhong C, Salyers A, et al. 2006. Comparison of antinociceptive actions of standard analgesics in attenuating capsaicin and nerve-injury-induced mechanical hypersensitivity. Neuroscience 143:587–596.
Jun JH, Yaksh TL. 1998. The effect of intrathecal gabapentin and 3-isobutyl gamma-aminobutyric acid on the hyperalgesia observed after thermal injury in the rat. Anesth Analg 86:348–354.
Karmakar MK, Ho AM. 2004. Postthoracotomy pain syndrome. Thorac Surg Clin 14:345–352.
Koehler RP, Keenan RJ. 2006. Management of postthoracotomy pain: Acute and chronic. Thorac Surg Clin 16:287–297.
Leslie RA, James MF. 2000. Pharmacological magnetic resonance imaging: A new application for functional MRI. Trends Pharmacol Sci 21:314–318.
Ling B, Authier N, Balayssac D, Eschalier A, Coudore F. 2007. Behavioral and pharmacological description of oxaliplatin-induced painful neuropathy in rat. Pain 128:225–234.
Lynch JJ III, Wade CL, Zhong CM, Mikusa JP, Honore P. 2004. Attention of mechanical allodynia by clinically utilized drugs in a rat chemotherapy-induced neuropathic pain model. Pain 110:56–63.
Melzack R. 1999. From the gate to the neuromatrix. Pain (Suppl) 6:S121–S126.
Moffitt PF, Kalucy EC, Kalucy RS, Baum FE, Cooke RD. 1991. Sleep difficulties, pain and other correlates. J Intern Med 230:245–249.
Morin CM, Gibson D, Wade J. 1998. Self-reported sleep and mood disturbance in chronic pain patients. Clin J Pain 14:311–314.
Nicholson B, Verma S. Comorbidities in chronic neuropathic pain. Pain Med 5(Suppl 1):S9–S27.
O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, Robinson ME. 2010. Negative mood mediates the effect of poor sleep on pain among chronic pain patients. Clin J Pain 26:310–319.
Pilowsky I, Crettenden I, Townley M. 1985. Sleep disturbance in pain clinic patients. Pain 23:27–33.
Ramesh, Shukla NK, Bhatnagar S. 2009. Phantom breast syndrome. Indian J Palliat Care 15:103–107.
Rice AS, Maton S. 2001. Gabapentin in postherpetic neuralgia: A randomized, double blind, placebo controlled study. Pain 94:215–224.
Ro LS, Chang KH. 2005. Neuropathic pain: Mechanisms and treatments. Chang Gung Med J 28:597–604.
Rorden C, Karnath HO. 2004. Using human brain lesions to infer function: A relic from a past era in the fMRI age? Nat Rev Neurosci 5:813–819.
Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. 1998. Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. JAMA 280:1837-1842.
Shih YY, Chen YY, Chen CC, Chen JC, Chang C, Jaw FS. 2008. Whole-brain functional magnetic resonance imaging mapping of acute nociceptive responses induced by formalin in rats using atlas registration-based event-related analysis. J Neurosci Res 86:1801–1811.
Shimoyama M, Shimoyama N, Hori Y. 2000. Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. Pain 85:405–414.
Stanfa LC, Singh L, Williams RG, Dickenson AH. 1997. Gabapentin, ineffective in normal rats, markedly reduces C-fiber evoked responses after inflammation. Neuroreport 8:587–590.
Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. 1991. Multiple representations of pain in human cerebral cortex. Science 251:1355–1358.
Treede RD, Kenshalo DR, Gracely RH, Jones AK. 1999. The cortical representation of pain. Pain 79:105–111.
Troels SJ, Nanna BF. 2009. Neuropathic pain treatment: A further step forward. Lancet 374:1218–1219.
Vecht CJ, Van de Brand HJ, Wjer QJ. 1989. Post-axillary dissection pain in breast cancer due to a lesion of the intercostobrachial nerve. Pain 38:171-176.
Wise RG, Rogers R, Painter D, Bantick S, Ploghaus A, Williams P, Rapeport G, Tracey I. 2002. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful

stimulation are specifically modulated by remifentanil. Neuroimage 16:999–1014.
Wise RG, Williams P, Tracey I. 2004. Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. Neuropsychopharmacology 29:626–635.
Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. 2007. Chemotherapy-evoked painful peripheral neuropathy: Analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. Neuroscience 144:714–720.
Zgierska A, Brown RT, Zuelsdorff M, Brown D, Zhang Z, Fleming MF. 2007. Sleep and daytime sleepiness problems among patients with chronic noncancerous pain reciving long-term opioid therapy: A cross-sectional study. J Opioid Manag 3:317–327.
Zhang RX, Lao L, Qiao JT, Malsnee K, Ruda MA. 2004. Endogenous and exogenous glucocorticoid suppresses up-regulation of preprodynorphin mRNA and hyperalgesia in rats with peripheral inflammation. Neurosci Lett 359:85–88.

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－

Phase Ⅲ Study on Control of Cancer Pain by HFT-290
－Dose-Conversion Confirmatory Study－

宮崎　東洋　　並木　昭義　　小川　節郎　　北島　敏光　　増田　豊
巌　　康秀　　内田　英二　　井関　雅子　　的場　元弘　　橋爪　隆弘

臨　床　医　薬
第26巻　第9号　別冊
平成22年9月発行

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－

Phase Ⅲ Study on Control of Cancer Pain by HFT-290
－Dose-Conversion Confirmatory Study－

宮崎 東洋[1)*] 並木 昭義[2)*] 小川 節郎[3)**] 北島 敏光[4)*] 増田 豊[5)*]
巌 康秀[6)*] 内田 英二[7)**] 井関 雅子[8)*] 的場 元弘[9)**] 橋爪 隆弘[10)*]

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

1）Toyo Miyazaki 東京クリニック 2）Akiyoshi Namiki 小樽市病院事業管理者 3）Setsuro Ogawa 日本大学医学部 麻酔科学 4）Toshimitsu Kitajima 獨協医科大学 麻酔科学 5）Yutaka Masuda 昭和大学薬学部 治療ニーズ探索学 6）Yasuhide Iwao 杏林大学医学部 麻酔科学 7）Eiji Uchida 昭和大学医学部 第二薬理学 8）Masako Iseki 順天堂大学医学部 麻酔科学・ペインクリニック 9）Motohiro Matoba 独立行政法人国立がん研究センター中央病院 緩和医療科・精神腫瘍科 10）Takahiro Hashizume 市立秋田総合病院 外科
＊：治験調整委員 ＊＊：医学専門家

臨床医薬 26 巻 9 号（9 月）2010