ORIGINAL ARTICLE

A Phase II, multicenter, randomized, double-blind, placebo-controlled crossover study of CJC-1008—a long-acting, parenteral opioid analgesic—in the treatment of postherpetic neuralgia

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ABSTRACT

Introduction: *CJC-1008 is a chemical modification of the opioid peptide dynorphin A (1-13) (Dyn A) that promotes dynorphin's covalent attachment to human serum albumin in vivo after administration, thus prolonging its duration of action. The primary objective of this study was to evaluate the preliminary efficacy and safety of CJC-1008 as compared with placebo in patients with postherpetic neuralgia (PHN).*

Methods: *Patients with PHN were assigned 1:1 to receive active study medication or placebo. After dosing, measurements were made every 15 minutes for the first hour; at two, three, four, six, and eight hours postdose; and during return visits to the study site after two, seven, and 28 days (as necessary), as well as during precrossover and exit visits. These measurements examined: 1) overall pain intensity, 2) pain intensity for each individual PHN type, 3) categorical overall pain intensity, 4) categorical pain relief, and 5) adverse events (AEs). When PHN pain intensity returned to baseline and/or at patients' first request for rescue analgesia other than acetaminophen (typically around 28 days after dosing but sometimes as soon as two days postdose), patients were to cross over to the alternative treatment and be monitored on the same schedule.*

Results: *A substantial placebo response was observed, but the analgesic effect observed in the active group was greater than that in the placebo group for the first eight hours. By 24 hours, the difference was not significant. A total of 29 out of 30 patients (96 percent) experienced at least one treatment-emergent AE during active drug treatment, while 14 of 27 patients (52 percent) reported such AEs during placebo treatment. Of the AEs occurring within the first eight hours after dosing, 97 percent were reported during treatment with active drug and 3 percent were reported during treatment with placebo. The majority of these AEs were mild in intensity.*

Discussion: *This study provides evidence of a greater analgesic effect when using CJC-1008 compared to placebo in patients with PHN. However, the effect only lasted through eight hours postdose and diminished by 24 hours. This study provides evidence of a peripheral action of dynorphin, since CJC-1008 does not cross the blood-brain barrier.*

Key words: CJC-1008, dynorphin, postherpetic neuralgia, placebo response

Conflict of interest: This study was funded by ConjuChem, Inc.

INTRODUCTION

Postherpetic neuralgia (PHN), the result of a complication from herpes zoster infection, is a common neuropathic pain syndrome that is easily diagnosed. There are typically three types of pain described in association with PHN: I) constant, deep, aching, steady, burning pain; II) spontaneous, intermittent, recurrent, "neuralgic," shooting or electric-shock-like pain; and III) superficial, sharp, radiating, burning, tender, dysesthetic, or itch-like sensation evoked by light pressure on the skin (allodynia).[1] Because of the stability of the pain of PHN, it is frequently used as a model for the evaluation of drugs' analgesic efficacy.

Dynorphin A (Dyn A) is a potent opioid agonist with morphine-like activity, but it is limited in its clinical utility

by a short half-life of several minutes.[2-4] CJC-1008 (ConjuChem Inc., Montreal, Quebec, Canada) is a chemical modification of the opioid peptide Dyn A(1-13) that promotes dynorphin's covalent attachment to human serum albumin (HSA) in vivo after administration. A chemical modification, using maleimidopropionic acid, to the core therapeutic moiety of Dyn A enables bonding to the free thiol on circulating HSA without interfering with the therapeutic activity of the Dyn A molecule. By bonding to circulating HSA, CJC-1008 has a significantly longer duration of action than free Dyn A, and its ability to cross the blood-brain barrier may be restricted, thus potentially limiting the side effects typically observed with opioids.

CJC-1008 has been demonstrated to be effective in a variety of animal models of pain, including the mouse acetic acid writhing test, mouse paw formalin test, and rat neuropathic pain test. However, no effect was seen in the mouse tail-flick study or rat tail radiant-heat test, suggesting restriction of the compound to peripheral circulation (data on file, ConjuChem, Inc.).[5] Accessibility of CJC-1008 to peripheral nerves is anticipated to depend upon albumin permeation, according to studies reported by Allen and Kiernan.[6]

Safety and tolerability of intravenous (IV) doses of CJC-1008 up to 3 mg/kg was demonstrated in a Phase I study in normal volunteers (data on file, ConjuChem, Inc.). Some subjects experienced hypotension that rapidly returned to normal after stopping the infusions. In addition, some reported urticaria and injection-site irritation that resolved shortly after completion of the infusions.

It is hypothesized that CJC-1008 will provide relief of PHN pain, with an improved safety profile and extended duration of action as compared to conventional opioids. The primary objective of this study was to evaluate the preliminary efficacy of a single dose of CJC-1008 as compared with placebo by measuring change in overall pain intensity over time (up to 28 days) in patients with PHN.

METHODS

This study was approved by the Human Subjects Committee at each participating institution. This was a Phase II, randomized, double-blind, placebo-controlled crossover study comparing the efficacy of a single IV dose of 3 mg/kg CJC-1008 to placebo in patients with PHN. Accepted patients met the following criteria: 1) men and women over the age of 18, 2) weight between 45 and 110 kg, 3) PHN for a minimum of three months following shingles (rash healing), and 4) minimum overall pain intensity of 45 out of 100 mm on the visual analog scale (VAS) at baseline. If overall pain intensity on the VAS was not at least 45 mm, a patient could still be eligible if the pain intensity for at least one of the three individual PHN pain types was at least 45 mm (see introduction for description of pain types). This qualifying pain type was designated as the "Index VAS" for that patient and would be used for further study assessments. Exclusion criteria included: 1) anesthetic nerve block within two weeks of study entry or any previous neurolytic nerve block in the area of PHN pain; 2) Karnofsky score < 60; 3) use of any nonopiate analgesic, unless taking a stable dose for at least 30 days prior to study entry; and 4) use of any psychoactive drug within 72 hours prior to study entry.

After meeting all eligibility criteria at screening (Visit 1), patients who were taking opiate analgesics entered a two-to-seven-day opiate-washout period. Following the washout period, patients with a minimum pain intensity score of 45 mm for overall pain intensity or at least one of the three types of PHN pain and who continued to meet all other eligibility requirements at the time of Visit 2 (baseline visit) were assigned 1:1 to receive either a) active study medication during the first treatment period, followed by blinded placebo during the second crossover treatment period; or b) the same two treatments in the reverse order.

Following randomization, patients received an infusion of study medication or placebo over 30 minutes in a monitored setting. After dosing, evaluations took place every 15 minutes for the first hour; at two, three, four, six, and eight hours postdose; and during return visits to the study site after two, seven, and 28 days (as necessary), as well as precrossover and exit visits. Evaluations performed at these time points included: 1) vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation), 2) overall pain intensity (100-mm VAS), 3) pain intensity (100-mm VAS) for each individual PHN type, 4) categorical overall pain intensity (6-point Likert), 5) categorical pain relief (6-point Likert), 6) AEs, 7) physical examination (selected time points), and 8) blood and urine samples for laboratory evaluations and pharmacokinetic assessments (selected time points). In addition, on day one (for both initial treatment and crossover), one 12-lead electrocardiogram (ECG) was obtained between 30 minutes and an hour after dosing, and blood was collected for coagulation panel two hours after dosing.

During the first week following dosing, AEs and general status were assessed by daily telephone follow-up on days when no study-site visit was scheduled. In addition, efficacy assessments (VAS and Likert) were made daily by the patient in a diary on days when no visit was scheduled.

When PHN pain intensity returned to baseline (typically around 28 days after dosing but sometimes as soon as two days postdose) and/or at patients' first request for rescue analgesia other than acetaminophen, patients were to cross over to the alternative treatment and be monitored on the same schedule.

The intent-to-treat (ITT) population consisted of all patients randomized in the study, whether or not they

Table 1. Demographic and baseline characteristics			
Trait	**Postherpetic pain population**		
	ITT, n = 32	**Safety, n = 30**	**Evaluable, n = 26**
Gender			
Female	14	12	9
Male	18	18	17
Age (years)			
Mean	69	69	70
SD	12	11	12
Minimum	39	39	39
Maximum	83	83	83
Baseline Index VAS score (mm)			
Mean	65.0	65.0	64.7
SD	15.9	15.9	15.9
Minimum	25.0	25.0	25.0
Maximum	96.0	96.0	96.0
Baseline pain intensity Likert score			
Mean	3.0	3.0	3.0
SD	0.7	0.7	0.6
Minimum	1.0	1.0	1.0
Maximum	4.0	4.0	4.0

received any study drug. The safety population consisted of all patients who received any dose of the double-blind study medication. The efficacy-evaluable population consisted of patients who met the crossover criteria after the first treatment period, received the crossover treatment, and had at least one post-treatment efficacy assessment in each treatment period. Patients who failed to meet crossover criteria or left the study after the first treatment were included in the ITT population but not the evaluable population. The statistical analyses for the primary efficacy variable (Index VAS pain intensity score) were performed for both ITT and evaluable populations. Only the evaluable population was used in the statistical analysis of the secondary efficacy variables (overall VAS pain intensity score, pain intensity VAS for each of the three PHN pain types, pain intensity Likert score, pain relief Likert score, and time to Index VAS score (predose) or first request for opioid rescue analgesia, whichever was shorter).

Demographic and other baseline characteristics were summarized by treatment sequence group using descriptive statistics. The analysis of variance (ANOVA) model was used to analyze VAS scores. Least-square means for change from predose scores by treatment was determined, and 95 percent confidence intervals were calculated. Pain intensity and pain relief Likert scores were analyzed using the Wilcoxon Signed-Rank test. Time to Index VAS score (predose) or first request for opioid rescue analgesia, whichever was shorter, was analyzed using the Kaplan-Meier survival analysis and log-rank test. The "last observation carried forward" approach was used for inputting sporadic missing values.

RESULTS

A total of 32 patients entered the study and were randomized to treatment from the four study centers (12 from Wallace, eight from Moulin, seven from Clark, and five from Wasserman). Thirty patients received study treatment, and 26 patients completed the study. The 30 patients who received the initial randomized study treatment were included in the safety analysis. The 26 patients who received the initial treatment followed by the crossover

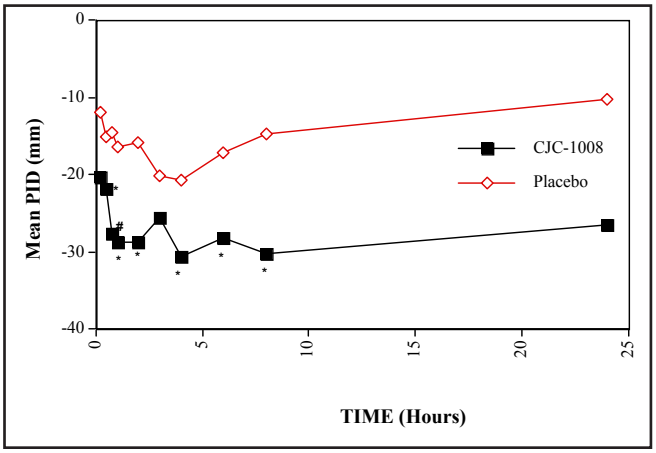

Figure 1. Line graph of the mean Index pain intensity difference (PID), in mm, from baseline through treatment period (0.25 to 24 hours); * p < 0.05, # P < 0.01.

treatment were included in the evaluable population. Demographic descriptions are summarized in Table 1.

The primary efficacy variable was the Index VAS score, which was the PHN pain score that qualified the patient for the study. Index VAS scores decreased immediately following treatment infusion and progressed through 24 hours postdose in both CJC-1008 and placebo groups. A substantial placebo response was observed during this period, but the analgesic effect observed in the active group (decrease of 21 to 31 mm) was greater than that observed with placebo (decrease of 11 to 21 mm). Other than the three-hour postdose time point, the reduction in the Index VAS scores was significantly greater following CJC-1008 administration than following placebo from predose through eight hours postdose. By 24 hours postdose, the difference between CJC-1008 and placebo was not significant. Most patients had pain intensity returning to baseline within 24 hours postdose and elected to cross over or exit within two days of treatment (Figure 1). A similar response was seen with the overall-pain intensity VAS scores (data not shown).

A similar postdose trend was present in VAS scores for both overall and Types I-III PHN. VAS scores for types I-III PHN exhibited very similar treatment effects as that observed in the Index VAS scores. With the exception of VAS scores at three hours postdose, CJC-1008 was significantly more effective at reducing the Type III PHN scores eight hours postdose (Figure 2C). A similar, but somewhat delayed, treatment effect was noted for Type I PHN scores (Figure 2A). Excluding the three-hour postdose time point, CJC-1008 was significantly more effective than placebo at reducing the patients' Type I PHN scores from 30 minutes postdose through the eight-hour postdose time point. CJC-1008 was significantly more effective than placebo in reducing Type II PHN pain intensity at 45 minutes and one hour postdose (Figure 2B). Despite these differences, no individual pain type was significantly more susceptible to the analgesic effects of CJC-1008.

The reduction in categorical pain intensity following administration of CJC-1008 was slightly greater than following placebo, with significant differences observed only at two and eight hours postdose. Patients reported slightly larger mean pain relief Likert scores following CJC-1008 than placebo, but the differences did not reach statistical significance (Figure 3). There were no significant treatment differences on the improvement of pain relief Likert scores between the two treatment groups.

PHN patients who reported drug-infusion-related AEs did not have pain intensity VAS or Likert scores significantly different from those who did not report these AEs.

Postdose time for first request of analgesia other than acetaminophen was analyzed using Kaplan-Meier techniques. Although the length of time to first request was longer following CJC-1008 (3.9 days) than placebo (2.3 days), no significant treatment effect was present, and the median length of time was not different between the two groups. Three patients reported complete and sustained pain relief for 28 days following treatment with CJC-1008, while no patients did so in the placebo group.

A total of 29 of the 30 patients in the study-drug group (96 percent) experienced at least one treatment-emergent AE during active drug treatment, while 14 of 27 patients (52 percent) reported such AEs during placebo treatment. Fifty-two percent of the AEs occurred within the first eight hours after dosing. Of the AEs occurring within the first eight hours, 97 percent were reported during treatment with active drug and 3 percent during treatment with placebo. The majority of these AEs were mild in intensity. Injection-site AEs were commonly reported during this study and were experienced exclusively by the active group (47 percent). Injection-site AEs included pain (30 percent), erythema (20 percent), burning (13 percent), pruritis (7 percent), coldness, paresthesias, and urticaria.[7] Other events reported in 10 percent or more of patients during CJC-1008 administration included dry mouth (67 percent), flushing (20 percent), headache (17 percent), erythema (13 percent), limb pain (13 percent), pruritis (13 percent), nausea (10 percent), conjuctival hyperemia (10 percent), and feeling hot (10 percent). After the first eight hours following infusion of CJC-1008, AEs reported in 10 percent or more of patients included dizziness (30 percent), headache (23 percent), nausea (23 percent), dry mouth (20 percent), constipation (17 percent), abdominal distension (10 percent), back pain (10 percent), influenza-like illness (10 percent), and limb pain (10 percent). No clinically significant abnormalities or trends were noted in the laboratory, vital sign, ECG, or physical examination findings.

DISCUSSION

PHN is a debilitating neuropathic pain syndrome that

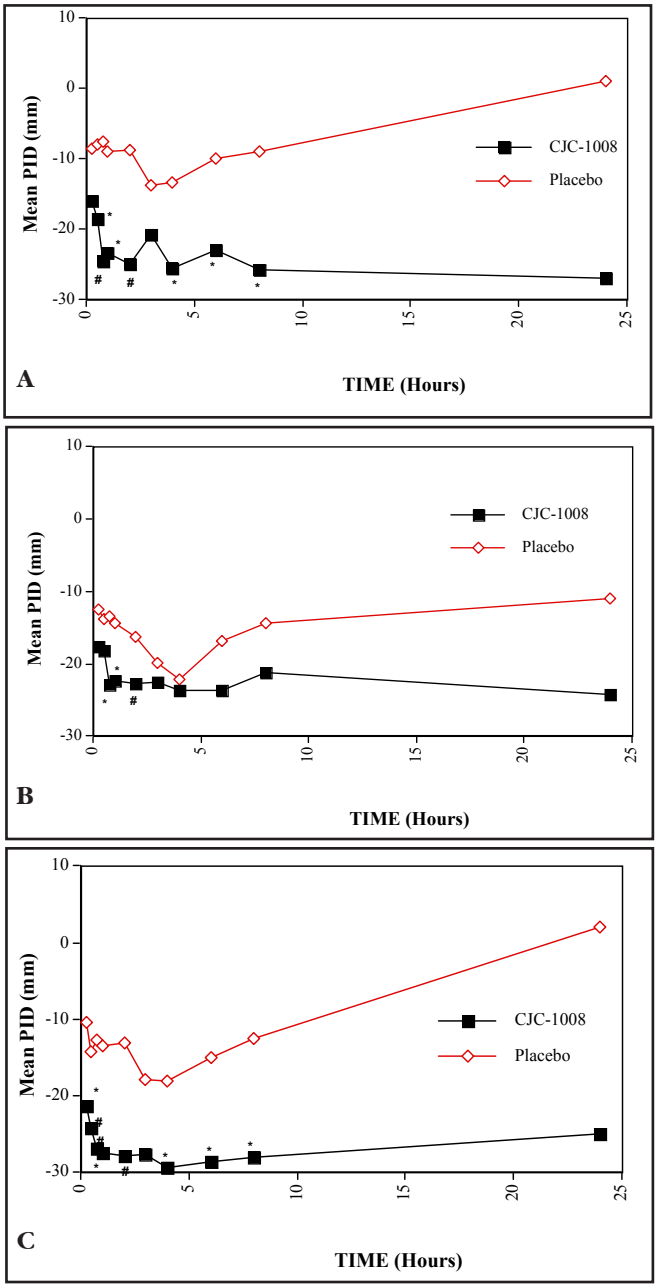

Figure 2. Line graph of the mean pain intensity difference (PID), in mm, of PHN Type I (A), Type II (B), and Type III (C) pain from baseline through treatment period (0.25-24 hours); * $p < 0.05$, # $P < 0.01$.

is often resistant to multiple therapies.[8] As such, it is often used for investigating new therapeutic interventions because it is a common pain syndrome that is readily distinguishable from other neuropathic pain conditions. Autopsy data from PHN patients have demonstrated chronic peripheral inflammation, as well as reduction of both axons and myelin in affected nerves.[9] Therefore, peripheral treatments may be effective. There are few treatments with proven efficacy, including gabapentin, pregabalin, lidoderm, and the tricyclic antidepressants.[10-13] However, there is emerging evidence that the opioids are effective in the treatment of this syndrome and can manage the pain chronically.[14]

Dyn A is an endogenous opioid peptide with both antinociceptive and pronociceptive properties. Dyn A was originally identified as an endogenous antinociceptive and analgesic molecule with activity at the kappa receptor.[15,16] However, more recent studies indicate that dynorphin has significant pronociceptive activity that is not mediated by opioid receptors.[17,18] This has led to mixed results when dynorphin is delivered into the central nervous system.[19,20]

Because of the mixed results with centrally delivered dynorphin, attention has been directed to the effect of endogenous ligands of peripheral opioid receptors. Many preclinical studies have demonstrated the presence of peripheral opioid receptors that, when occupied, decrease the excitability of sensory nerves by decreasing the release of excitatory substances from sensory nerves.[21,22] In addition, opioid peptides, including dynorphin, have been detected in immune cells within inflamed tissue in animals and humans.[22-24] It has been demonstrated that, when released, dynorphin can occupy opioid receptors on nerve endings and effect analgesia.[24] In addition, preclinical models on nociception have demonstrated a peripheral mechanism of action of dynorphin.[25,26] Therefore, there is reason to believe that dynorphin can exert analgesia through a peripheral mechanism.

This is the first clinical study to suggest that dynorphin has a peripheral analgesic action. Although we did not reach our primary efficacy endpoint of extended analgesia, we were able to demonstrate that conjugated dynorphin was analgesic and effected a prolonged analgesia of up to 24 hours. There are several explanations for the lack of extended analgesia. Well-known side effects of the opioids, mediated centrally, include respiratory depression, dependence, sedation, itching, nausea, and dysphoria. By limiting the opioid to the periphery, these side effects should be averted. However, on review of the side effects observed in our study, dizziness (30 percent) and nausea (23 percent) appeared after the first eight hours of the infusion. Side effects reported in the literature during treatment with Dyn A include paresthesia, dizziness, pruritis, headache, nausea, depression, somnolence, dry mouth, and chest palpitations.[27-30] Many of the side effects of Dyn A are thought to be mediated by histamine release, a known effect of opioids.[31,32] Therefore, the side effects observed in our study could result without central nervous system penetration. However, it is possible that, over time, the conjugated Dyn A molecule may penetrate into the central nervous system as albumin slowly equilibrates between the two compartments. If this occurs, then the central pronociceptive effects of dynorphin could counteract the peripheral antinociceptive

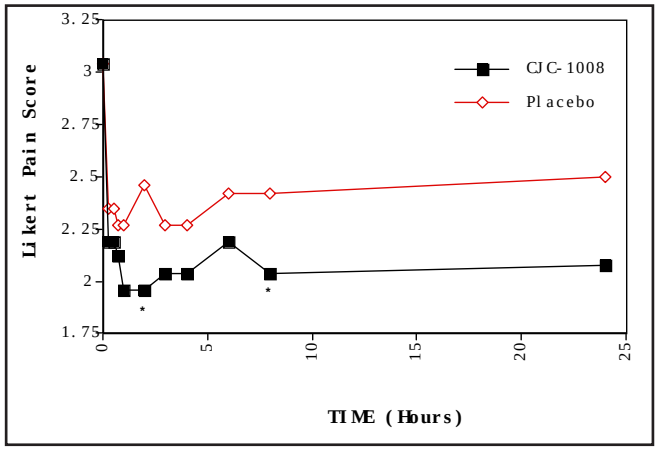

Figure 3. Line graph of the mean pain intensity Likert scale during treatment period (0-24 hours); * p < 0.05.

effects, accounting for the loss of analgesia at 24 hours. In addition, there are recent reports of acute tolerance to short-term delivery of potent opioid agonists, which could also explain the short duration of action.[33] It is unlikely that the dynorphin molecule was released from the albumin complex, since the free dynorphin would be broken down within minutes before it could penetrate the central nervous system. Given the side effects that we observed with CJC-1008, it is unlikely that the duration can be extended by increasing the dose, though the possibility exists to enhance efficacy through delivery of additional doses that may have a cumulative effect.

Another possible explanation for lack of extended duration is the study population we chose. Although PHN patients share a common etiology of pain, it has been suggested that there are actually three categories of pain mechanism.[1] Some patients have an "irritable nociceptor" and report pain relief with local infiltration, suggesting a peripheral mechanism. The other two categories are patients with deafferentation with and without allodynia. These patients do not respond to local infiltration, suggesting a central mechanism. The Type III patients in our study all suffered from allodynia; therefore, they would most likely correlate with the irritable-nociceptor theory. Although there was a trend for these subjects to report more pain relief than those of Types I and II, there was no statistical significance. In addition, there was no correlation between pain type and response seen in the three subjects who experienced sustained pain relief.

This was a proof-of-concept study that sought to demonstrate a prolonged analgesia with conjugated Dyn A. Although the duration of analgesia seen with CJC-1008 (between eight and 24 hours) was not as long as predicted, the duration of analgesia was much longer than that seen with free Dyn A (minutes). This study confirms that an albumin-conjugated drug-affinity complex can lead to sustained circulation without loss of parent pharmacologic activity.

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REFERENCES

1. Fields HL, Rowbotham M, Baron R: Postherpetic neuralgia: Irritable nociceptors and deafferentation. *Neurobiol Dis*. 1998; 5(4): 209-227.
2. Greenwald MK, Stitzer ML, Haberny KA: Human pharmacology of the opioid neuropeptide dynorphin A (1-13). *J Pharmacol Exp Ther*. 1997; 281: 1154-1163.
3. Chou JZ, Chait BT, Wang R, et al.: Differential biotransformation of dynorphin A (1-17) and dynorphin A (1-13) peptides in human blood, ex vivo. *Peptides*. 1996; 17: 983-990.
4. Muller S, Hochhaus G: Metabolism of dynorphin A 1-13 in human blood and plasma. *Pharm Res*. 1995; 12: 1165-1170.
5. Irwin S, Houde RW, Bennett DR, et al.: The effects of morphine, methadone and meperidine on some reflex responses of spinal animals to nociceptive stimulation. *J Pharmacol Exp Ther*. 1951; 101: 132-143.
6. Allen DT, Kiernan JA: Permeation of proteins from the blood into peripheral nerves and ganglia. *Neuroscience*. 1994; 59: 755-764.
7. Lynch JJ III, Jarvis MF, Kowaluk EA: An adenosine kinase inhibitor attenuates tactile allodynia in a rat model of diabetic neuropathic pain. *Eur J Pharmacol*. 1999; 364(2-3): 141-146.
8. Portenoy RK, Duma C, Foley K: Acute herpetic and postherpetic neuralgia: Clinical review and current management. *Ann Neurol*. 1986; 20: 651-664.
9. Portenoy RK: Neuropathic pain. In Portenoy RK, Kanner RM (eds.): *Pain Management: Theory and Practice*. Philadelphia: FA Davis Co., 1996.
10. Galer BS, Rowbotham MC, Perander J, et al.: Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: Results of an enriched enrollment study. *Pain*. 1999; 80: 533-538.
11. Dworkin RH, Corbin AE, Young JP Jr, et al.: Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology*. 2003; 60: 1274-1288.
12. Rowbotham M, Harden N, Stacey B, et al.: Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA*. 1998; 280: 1837-1863.
13. Max MB: Treatment of post-herpetic neuralgia: Antidepressants. *Ann Neurol*. 1994; 35: S50-S53.
14. Pappagallo M, Campbell JN: Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. *Ann Neurol*. 1994;

35: S54-S56.
15. Herz A: Multiple opiate receptors and their functional significance. *J Neural Transm Suppl*. 1983; 18: 227-233.
16. Przewlocki R, Stala L, Greczek M, et al.: Analgesic effects of mu-, delta- and kappa-opiate agonists and, in particular, dynorphin at the spinal level. *Life Sci*. 1983; 33(suppl. 1): 649-652.
17. Vanderah TW, Ossipov MH, Lai J, et al.: Mechanisms of opioid-induced pain and antinociceptive tolerance: Descending facilitation and spinal dynorphin. *Pain*. 2001; 92(1-2): 5-9.
18. Ossipov MH, Kovelowski CJ, Wheeler-Aceto H, et al.: Opioid antagonists and antisera to endogenous opioids increase the nociceptive response to formalin: Demonstration of an opioid kappa and delta inhibitory tone. *J Pharmacol Exp Ther*. 1996; 277(2): 784-788.
19. Knox RJ, Dickenson AH: Effects of selective and non-selective kappa-opioid receptor agonists on cutaneous C-fibre-evoked responses of rat dorsal horn neurones. *Brain Res*. 1987; 415: 21-29.
20. Willcockson WS, Kim J, Shin HK, et al.: Actions of opioids on primate spinothalamic tract neurons. *J Neuroscience*. 1986; 6: 2509-2520.
21. Stein C: Peripheral mechanisms of opioid analgesia. *Anesth Analg*. 1993; 76(1): 182-191.
22. Hassan AH, Przewlocki R, Herz A, et al.: Dynorphin, a preferential ligand for kappa-opioid receptors, is present in nerve fibers and immune cells within inflamed tissue of the rat. *Neurosci Lett*. 1992; 140(1): 85-88.
23. Stein C, Hassan AH, Przewlocki R, et al.: Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proc Natl Acad Sci U S A*. 1990; 87(15): 5935-5939.
24. Cabot PJ, Carter L, Schafer M, et al.: Methionine-enkephalin- and Dynorphin A-release from immune cells and control of inflammatory pain. *Pain*. 2001; 93(3): 207-212.
25. Beyer A, Schafer M, Stein C: Antinociceptive effects of dynorphin peptides in a model of inflammatory pain. *Pain*. 1997; 70(2-3): 141-147.
26. Shibata M, Ohkubo T, Takahashi H, et al.: [Peripheral analgesic actions of opioid peptides and morphine analogues]. *Nippon Yakurigaku Zasshi*. 1986; 88(2): 101-107.
27. Kreek MJ, Schluger J, Borg L, et al.: Dynorphin A1-13 causes elevation of serum levels of prolactin through an opioid receptor mechanism in humans: Gender differences and implications for modulation of dopaminergic tone in the treatment of addiction. *J Pharmacol Exp Ther*. 1999; 288: 260-269.
28. Wen HL, Ho WK: Suppression of withdrawal symptoms by dynorphin in heroin addicts. *Eur J Pharmacol*. 1982; 82: 183-186.
29. Specker S, Wananukul W, Hatsukami D, et al.: Effects of dynorphin A(1-13) on opiate withdrawal in humans. *Psychopharmacology*. 1998; 137: 326-332.
30. Gambus PL, Schnider TW, Minto CF, et al.: Pharmacokinetics of intravenous dynorphin A(1-13) in opioid naive and opioid-treatment human volunteers. *Clin Pharmacol Ther*. 1998; 64: 27-38.
31. Barke KE, Hough LB: Simultaneous measurement of opiate-induced histamine release in the periaqueductal gray and opiate antinociception: An in vivo microdialysis study. *J Pharmacol Exp Ther*. 1993; 266: 934-942.
32. Barke KE, Hough LB: Opiates, mast cells and histamine release. *Life Sci*. 1993; 53: 1391-1399.
33. Gustorff B, Nahlik G, Hoerauf KH, et al.: The absence of acute tolerance during remifentanil infusion in volunteers. *Anesth Analg*. 2002; 94(5): 1223-1228, table of contents.