Short- and intermediate-term efficacy of buprenorphine TDS in chronic painful neuropathies

Paola Penza¹, Angela Campanella¹, Alfredo Martini², Giorgia Melli¹, Raffaella Lombardi¹, Francesca Camozzi¹, Grazia Devigili³, and Giuseppe Lauria¹

¹Neuromuscular Diseases Unit and ²Research and Development Unit, Fondazione IRCCS National Neurological Institute “Carlo Besta”, Milan; and ³Neurological Clinic, University of Ferrara, Ferrara, Ferrara Italy

Abstract  Buprenorphine is a potent opioid available as a transdermal delivery system (TDS) formulation. This open-label study investigated its safety, tolerability, and efficacy in 30 patients with chronic painful neuropathy. Subjects with visual analogue scale (VAS) score ≥5 under stable analgesic treatment were entered. The starting dosage of 35 µg/h was increased up to 70.0 µg/h in case of unsatisfactory pain control as assessed by fortnightly visits. The primary endpoint was the number of patients achieving at least 30% pain relief at day 42 visit. Treatment was safe over the study period. Nine patients dropped out for side effects, mostly nausea and daily sleepiness. Buprenorphine TDS was well tolerated in 21 patients. Thirteen patients achieved >30% of pain relief at day 42 visit. Five patients needed to increase the dosage to 52.5 µg/h. Eight patients did not meet the primary outcome, but none allowed increasing the dosage to 70 µg/h, and four patients withdrew consent to continue the study before day 42 visit because of a ‘fear to become addicted,’ although 40% had obtained VAS reduction. In our study, which needs to be confirmed by a controlled trial, buprenorphine TDS induced clinically meaningful pain relief in about 40% of patients with chronic painful neuropathy, suggesting its use as a third-line treatment.

Key words: buprenorphine, nerve conduction studies, neuropathic pain, opioids, pain relief, painful neuropathy, peripheral neuropathies, treatment

Introduction  Neuropathic pain remains a therapeutic challenge in clinical practice. Despite the increasing knowledge of the pathophysiology of neuropathic pain, the approach to treatment remains non-specific and disappointing (Baron, 2006). Responses to treatments are variable and unpredictable, and the optimum dose for a particular drug may vary from patient to patient. Current treatments achieve a 50% reduction in pain intensity in only 25–50% of patients (England and Gould, 2002; Attal et al., 2006). Painful neuropathies represent a common cause of chronic neuropathic pain that affect the quality of life of patients. Despite different etiologies such as diabetes, HIV, or chemotherapy, painful neuropathies share clinical features and approaches to treatment. It has been suggested that effective treatments in one diagnostic entity can be used for other etiologies of painful neuropathy (Hansson and Dickenson, 2005), with the exception of HIV-related neuropathy that is usually less responsive.
(Finnerup et al., 2005). Recent guidelines suggest opioids as second- or third-line treatments for painful neuropathies after antidepressant or anti-epileptic drugs (Attal et al., 2006). Combination therapy deserves particular interest because of potential synergic effects, but their efficacy has been assessed in only a few studies combining anticonvulsants with opioids or antidepressants (Gilron et al., 2005; Hanna et al., 2008).

Although opioids can provide effective pain relief in patients with neuropathic pain caused by central or peripheral nervous system injuries (Finnerup et al., 2005), data on effectiveness in painful peripheral neuropathies are limited to oxycodone and tramadol (Attal et al., 2006; Hanna et al., 2008). Buprenorphine is an effective and well-tolerated analgesic in the treatment of malignant and non-malignant chronic pain (Griessinger et al., 2005). Its usefulness in neuropathic pain has been demonstrated in experimental models (Christoph et al., 2005) and clinical studies (Hans, 2007). Buprenorphine has a good safety profile in animals and humans (Dahan et al., 2005), and the transdermal administration route offers several potential advantages over the parenteral and oral routes. However, data relevant to the analgesic activity of buprenorphine in patients affected by painful neuropathy are scant.

The aim of this open-label study was to investigate the pain relief of buprenorphine transdermal delivery system (TDS) in patients with inadequately controlled chronic neuropathic pain caused by painful neuropathy. Secondary aims were the assessment of optimal dose schedule and side effects.

Materials and Methods

We recruited patients with a diagnosis of peripheral neuropathy based on clinical and neurophysiological criteria with at least 6 months of inadequately controlled neuropathic pain. Patients must have a visual analogue scale (VAS) score \( \geq 5 \), and no condition known to hinder the assessment of efficacy and tolerability. VAS score was obtained by asking patients to grade the mean severity of pain during the past 24 h using a 10-cm line with no anchors on which the ends indicate ‘no pain’ and ‘worst possible pain.’ Exclusion criteria were known hypersensitivity to opioids, history of alcohol or drug abuse, treatment with opioids within the past 2 months, treatment with monoamine oxidase inhibitors within the past 2 weeks, conditions known to be at risk for respiratory failure, previous diagnosis of myasthenia gravis, delirium tremens, epileptic attacks, psychiatric disorders, liver function disorders, and participation in a clinical trial for neuropathic pain within 3 months prior to the screening. At the screening visit, all patients underwent the Beck Depression Inventory scale, and patients with a score higher than 13 were excluded from the study. The study was funded by the National Neurological Institute “Carlo Besta” and approved by the local ethic committee. Patients were included after giving written informed consent.

The primary outcome measure was the number of individuals achieving at least 30% of pain severity comparing the baseline and day 42 visit VAS. Secondary outcome included the Patient Global Impression of Change (PGIC), the quality of sleep assessed by the Short Sleep Quality Questionnaire (SQRNS), and the reduction of pretrial analgesic medications. Safety was assessed by routine hematological tests and adverse events.

All patients were asked to maintain a stable regimen of pretrial analgesic medications in order to analyze the efficacy of buprenorphine TDS as add-on therapy. Patients who had already withdrawn from previous treatments (e.g., antidepressants or anti-epileptics) for at least 4 weeks were given buprenorphine TDS as monotherapy.

In the initial protocol, buprenorphine TDS was started at a dose strength of 35 \( \mu g/h \). However, at that dose, four of the first six patients dropped out for side effects during the first week (see below). The protocol was then changed to begin buprenorphine TDS at 8.75 \( \mu g/h \) (one-fourth of patch) and increase by 8.75 \( \mu g/h \) (one-fourth of patch) every 3 days until reaching 35 \( \mu g/h \) (one patch). This dose was continued for 2 weeks, and if patients did not achieve a 30% reduction in VAS scores, the dose could be increased to 52.5 \( \mu g/h \) and then to 70 \( \mu g/h \) at 2-week intervals for a total of 6 weeks of treatment. The TDS was changed every 72 h during the trial. Patients were then followed for further 4 weeks. During the dose titration phase, those on prior analgesic medications remained on stable doses. Patients who did not show an analgesic response at the 70 \( \mu g/h \) dose strength by day 42 visit were considered non-responders and were dropped. Metoclopramide (10 mg by oral route up to three times a day) was allowed to control nausea. VAS, SQRNS, and PGIC were administered at the screening visit and fortnightly at each clinic visit during the study period until day 70 visit.

Results

Clinical features and etiology of neuropathy

Thirty subjects were included – 17 women and 13 men, mean age 58.3 years; range 38–75 years (Table 1). The etiological diagnosis of the neuropathy was determined in 17 patients, whereas in 13 patients,
Table 1. Clinical features and response to treatment with buprenorphine TDS in 30 patients with chronic painful neuropathy. VAS reduction was calculated as the percentage between score at screening and at day 42. Dropout was due to side effects (patient no. 22–30) or withdrawal of consent (patient no. 18–21). Patient no. 12–15 did not achieve 30% VAS reduction (non-responders).

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<th>Buprenorphine (daily dose, μg/h)</th>
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<th>VAS at day 28</th>
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(continued)
it remained unknown after screening for diabetes, impaired glucose tolerance, vitamin deficiencies, viral infections, systemic immune-mediated disorders, and malignancies.

Tolerability

Nine patients (no. 22–30) discontinued treatment because of side effects, the most common of which were nausea and daytime sleepiness (seven patients). Three patients reported constipation, three had hypotension, two experienced urinary retention, and one complained of paradoxical hyperalgia. Four of these nine patients had started buprenorphine TDS at the full dose strength of 35 μg/h and dropped out during the first week for side effects. Five patients had titrated buprenorphine by 8.75 μg/h (one-fourth of patch) every 3 days up to 35 μg/h but did not further tolerate the treatment and dropped out during the first 2 weeks.

Efficacy of treatment

Thirteen patients (no. 1–11, 16, and 17) met the primary outcome and achieved a reduction in VAS score of >30% at day 42 visit compared with the screening visit. Ten of them (no. 3–11 and 17) achieved >30% of pain relief at the day 14 visit, 1 patient (no. 16) at day 28, and 2 patients (no. 1 and 2) at day 42. Five patients (no. 9–11, 13, and 16) needed to increase the dose of buprenorphine TDS to 52.5 μg/h, three of them (no. 9, 13, and 16) at day 14, and two of them (no. 10 and 11) at day 28 visit.

Eight patients (no. 12–15 and 18–21) did not meet the primary endpoint of a reduction in VAS score of >30% at day 42 visit. Only four patients (no. 12–15) could be followed until day 70 visit, and none of them consented to increase the dosage of buprenorphine TDS to 70 μg/h. Four patients withdrew consent to continue the study: two of them (no. 18 and 21) at day 28 and day 14, respectively because they did not achieve satisfactory pain relief and two patients (no. 19 and 20) at day 28 because of a ‘fear to become addicted,’ although they had achieved >30% of VAS reduction (Table 1). PGIC improved insignificantly over the study period. Quality of sleep also did not change during the study.

Discussion

The management of painful neuropathies remains a challenge in clinical practice for several reasons. First, about 50% of patients cannot achieve satisfactory pain relief. Second, the current approach to symptoms is non-specific. Third, most of the drugs
available in the category of antidepressant and anticonvulsant do not significantly differ from each other in terms of efficacy and prevalence of side effects, although few comparator studies are available. Last, there are few studies of combined treatments.

The use of opioids in non-malignant neuropathic pain has been controversial for a long time (Carver and Foley, 2001). However, recent studies have indicated that they can induce analgesia in non-malignant conditions (Kalso et al., 2004). The recent guidelines of the European Federation of the Neurological Societies supported their use as second- or third-line choice in painful peripheral neuropathies, though data are limited to oxycodone and tramadol (Attal et al., 2006). Moreover, only a few studies have included a homogenous population of patients, leaving the issue of the balance between safety and efficacy unaddressed (Eisenberg et al., 2005; Cruccu, 2007). Interestingly, a randomized, placebo-controlled study in painful diabetic neuropathy and post-herpetic neuralgia demonstrated that the use of morphine in combination with gabapentin allowed achieving better analgesia at lower doses of each drug than either as a single agent (Gillon et al., 2005).

Buprenorphine acts as partial agonist at µ-opioid receptor and antagonist at κ-opioid and δ-opioid receptors. Its systemic potency is 25–50 times that of morphine (Leander, 1988), and it has a longer duration of action compared with other lipophilic opioids because of the high affinity for µ-opioid receptor (Yaksh, 1981). The recent availability of the TDS preparation has facilitated its use because the release of the drug does not depend on a rate-controlling membrane, as in reservoir-type patches, so in the case of damage to the patch, there is no risk of excessive overdose or ‘dose dumping.’ Moreover, the TDS preparation allows slow increments of dosage by cutting the patch and gives a relatively constant serum concentration of the drug over a predictable period of time (Budd, 2003). Buprenorphine may have some advantages over other opioids used in clinical practice, including the absence of interference with immune responses (Martucci et al., 2004), the ceiling effect for respiratory depression but not for analgesia that gives a greater margin of safety (Dahan et al., 2005; 2006), and the lower risk of drug dependence or tolerance development due to the absence of receptor internalization and high dose stability (Evans and Easthope, 2003; Simonnet, 2005).

Randomized controlled trials have already demonstrated efficacy and safety of buprenorphine TDS in non-malignant conditions (Bohme, 2002; Sorge and Sittel, 2004), but no data on painful neuropathies are available. In our series, buprenorphine TDS reduced the intensity of pain by at least 30%, a change perceived as clinically meaningful (Farrar et al., 2001), in about 40% of patients. Interestingly, most responder patients achieved satisfactory pain relief within 2 weeks from the beginning of treatment and at the dosage of 35 µg/h. However, the open-label design of the study could have overestimated its effect in responders, and our results should be confirmed by a controlled clinical trial. Side effects represented a major limiting problem, causing the withdrawal of treatment in 30% of patients, a percentage similar to that reported with other opioids (Kalso et al., 2004). Side effects, characterized by nausea and daytime sleepiness in most patients and by hypotension in some of them, were frequent and severe, starting at the lowest available dosage of 35 µg/h. A slower titration of the drug by increasing the dosage by one-fourth of the patch every 72 h reduced their frequency. Two patients decided to withdraw treatment before reaching the last follow-up visit because of a fear to become addicted, despite achieving satisfactory pain control. This finding can be considered a further limitation of chronic treatment with opioids and should be kept into consideration in clinical practice.

Randomized controlled trials vs. placebo or active drugs to test the efficacy of opioids in painful neuropathies can be limited by a number of reasons. Systemic side effects, occurring in at least 30% of patients, can interfere with blinding. Patients with long-standing neuropathic pain, unresponsive to first- and second-line treatments, require major efforts to achieve satisfactory pain relief and are unlikely to accept inclusion in a placebo arm or to undergo treatment with a class of drugs that are already proven to be ineffective. Open-label studies have intrinsic limitations, but they can contribute in providing useful information for future trials. Our study suggests that future trials should start buprenorphine TDS at 8.75 µg/h and titrate slowly in order to reduce the frequency of side effects.

We found that buprenorphine TDS can induce a clinically meaningful decrease of pain intensity in about 40% of patients, in most of them at the dosage of 35 µg/h for a period of 10 weeks. However, the prevalence of non-responder and dropout patients was higher than that of responders, emphasizing the relative weight of poor tolerability comparing with efficacy.

References