Efficacy and Safety of Transdermal Buprenorphine: A Randomized, Placebo-Controlled Trial in 289 Patients with Severe Cancer Pain

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Abstract

Strong opioids are recommended for treating severe cancer pain in the advanced stages of the disease. Few data are available concerning the efficacy of buprenorphine in cancer pain. We compared transdermal buprenorphine 70 μg/h (BUP TDS) to placebo in an enriched design study. Opioid-tolerant patients with cancer pain requiring strong opioids in the dose range of 90–150 mg/d oral morphine equivalents entered a two-week run-in phase, during which they were converted to BUP TDS. Patients who could be stabilized on BUP TDS were randomized to BUP TDS or placebo patch for a two-week maintenance phase. Rescue medication (buprenorphine sublingual tablets 0.2 mg) was allowed as required. Response was defined as a mean pain intensity of < 5 (0–10 scale) and a mean daily buprenorphine sublingual tablet intake of ≤ 2 tablets during the maintenance phase. Of 289 patients who entered the run-in phase, 100 discontinued treatment due to lack of efficacy or adverse events; 189 patients continued treatment in the maintenance phase (94 BUP TDS, 95 placebo), of whom 31 discontinued treatment (7 BUP TDS, 24 placebo). A significant difference in the number of treatment responders was observed: 70 BUP TDS (74.5%, 65.7–83.3) vs. 47 placebo (50%, 39.9–60.1) (P = 0.0003). This result was supported by a lower daily pain intensity, lower intake of buprenorphine sublingual tablets and fewer dropouts in the BUP TDS group. The incidence of adverse events was slightly higher for BUP TDS. In conclusion, BUP TDS 70 μg/h is an efficacious and safe treatment for patients with severe cancer pain.

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Pain, cancer, buprenorphine, transdermal, placebo, enriched design

Introduction
More than nine million patients worldwide suffer from cancer pain, which is mostly caused by the cancer itself or by cancer-related therapy. With metastatic cancer or advanced disease, the prevalence of pain may exceed 67% of all patients.1 Despite considerable advances, cancer pain often remains undertreated.2 Psychological influences on the perception of pain and on opioid efficacy itself are evident.3 Devising an individualized evidence-based therapy is complicated by a general lack of randomized controlled trials in palliative care pain patients, which may be mainly due to ethical considerations and methodological problems, such as low trial sensitivity, small sample sizes, and lack of standardized efficacy measures.4

Despite being termed the “gold standard,” even the prescription of morphine is limited by great variability in dose requirements and response.5 Its use may be complicated by the accumulation of morphine metabolites, leading to dose reduction or opioid rotation, in renally impaired, elderly, or high-dose patients.6 By contrast, buprenorphine (BUP) shows no clinically relevant accumulation of active metabolites,7 and pharmacokinetics remain unchanged in renal insufficiency.8 BUP might, therefore, be used as an alternative in these compromised patients.9

BUP, a partial agonist at the μ- and antagonist at the κ-opioid receptor,10 has been available for >25 years in sublingual and parenteral formulations, and has a well-established efficacy and safety profile.11 According to the World Health Organization, BUP is recommended as a strong opioid on Step 3 of the analgesic ladder for cancer pain relief. The recently developed transdermal (TDS) formulation was introduced in Europe in 2001, and available patches release BUP at three different rates: 35 μg/h, 52.5 μg/h, and 70 μg/h, corresponding to daily doses of 0.8 mg, 1.2 mg, and 1.6 mg, respectively. BUP TDS is indicated for moderate to severe cancer and noncancer pain that does not respond to nonopioid analgesics. Incident or breakthrough pain caused by underlying disease can be treated by the concomitant administration of BUP sublingual (BUP SL) tablets (0.2 mg). Although considerable experience has been gained with various formulations of BUP in patients requiring strong analgesia,12 data on the use of BUP TDS in treating severe cancer pain are limited. The aim of this study was to investigate the analgesic efficacy and safety of the largest available BUP TDS patch (70 μg/h) in patients with severe chronic cancer pain.

Methods
Patient Selection
A total of 289 patients were recruited between February 2004 and January 2005 from 26 centers in Austria, Belgium, Croatia, France, Poland, and The Netherlands. Patients with documented malignant disease and insufficient pain relief from their current opioid regimen were eligible. Patients were receiving single opioids or combination therapy, including oral morphine 90−150 mg/day (n = 105), transdermal fentanyl 25−50 μg/h (n = 170), tramadol 400−600 mg (n = 75), hydromorphone 8−16 mg (n = 6), or oxycodone 40−60 mg (n = 5). A protocol for chemotherapy or radiotherapy could be applied concomitantly. Adjuvant analgesics (tricyclic antidepressants, benzodiazepines, anticonvulsants, muscle relaxants, and corticosteroids) were allowed, providing the dose was stable.

Each center obtained approval from national or regional ethical committees, and all patients gave informed written consent before entering the study.

Treatment
A randomized, double-blind, placebo-controlled enrichment design was applied. Randomization was performed in blocks with a 1:1 ratio (BUP TDS: placebo). Hospital pharmacies received coded study medication from the sponsor and delivered the blinded supply for each patient. BUP TDS and placebo
patches were identical in appearance and adhesive properties. The randomization list was stored in a sealed, nontransparent envelope and the code was not broken until the database had been locked.

Eligible patients first entered an open-label, two-week run-in phase. Previous centrally- and peripherally-acting analgesics were stopped and patients were converted to a 70 µg/h BUP TDS patch, applied every three days (Transtec 70 µg/h, Grünenthal). Anticonstipation and antiemetic treatment could be continued, and/or adjusted.

At the end of the run-in phase, patients responding to BUP TDS, that is, who had a mean pain intensity (PI) of <5 on a 0–10 scale and a mean intake of ≤2 tablets of BUP SL over the last four days, were allocated to BUP TDS or placebo treatment for a double-blind, two-week maintenance phase. Rescue medication (BUP sublingual tablets 0.2 mg, Temgesic, Schering Plough) was allowed as needed for breakthrough pain during both phases of the study.

Assessments

The primary outcome measure was the percentage of patients classified as responders, that is, those who had a mean PI of <5 during the last six days of the maintenance phase and a mean daily BUP SL intake of ≤2 tablets over the entire maintenance phase. Patients reported their current pain twice daily using a 0–10 scale by answering the question “Please rate your pain by circling the one number that tells how much pain you have right now” (0 = No pain, 10 = Pain as bad as you can imagine).

Secondary efficacy outcome measures were the course of daily PI, the amount of BUP SL taken, and the patients’ global satisfaction with treatment on a five-point scale (excellent, very good, good, fair, or poor).

The safety assessments were based on patient-reported adverse events. At each visit, the patient was asked by the investigator for the occurrence of any adverse event, which was directly documented in the Case Record Form. Additionally, withdrawals due to adverse events or lack of efficacy were analyzed.

Statistical Analysis

The sample size was based on the primary outcome measure specified as the difference in response rates between treatment groups. The clinically relevant difference was defined as ≥25%, as reported in a previous study. A Fisher’s exact test with a power of 0.90 and a level of significance of 0.05 required 88 patients per treatment group for the maintenance phase of the study. Allowing for an expected run-in discontinuation rate of 30% required a sample of at least 250 patients. The post hoc power analysis with response rates of 75% for active, 50% for placebo and n = 94 per group, would lead to power of 94%.

Response rates are given as percentages. All other data are given as absolute (relative) numbers, means and 95% confidence intervals, or means and standard errors. For the primary outcome measure, treatment groups were compared using a Cochran-Mantel-Haenszel test adjusting for the individual center. For the secondary outcome measures, pain intensity and rescue medication were compared using an analysis of covariance model that included fixed effects for baseline pain intensity (average pain intensity on the four days preceding randomization visit), treatment and centers. Significance was defined as a P-value of 0.05 or less.

Results

Patients

The demographic characteristics of the run-in population were similar to the randomized group of patients. Most patients were suffering from pain related to multiple metastases. At randomization, the two study groups had comparable pain intensity and consumption of rescue medication (Table 1).

Of the 289 enrolled patients, 92 (32%) discontinued BUP TDS treatment and 8 (3%) died during the run-in phase. Of the 189 (65%) patients responding to BUP TDS (≤2 tablets of BUP SL/day, mean pain intensity <5 points) and who were allocated to study medication, seven discontinued BUP TDS treatment and 24 discontinued placebo treatment (Fig. 1).

Treatment Effects on Pain Intensity

Of 188 patients analyzed for efficacy in the maintenance phase (94 BUP TDS, 94 placebo), 70 in the BUP TDS group (74.5%; 65.7–83.3) vs. 47 in the placebo group
(50.0%; 39.9–60.1) were responders. The observed difference in response rates was statistically significant ($P = 0.0003$).

During the run-in phase, PI for the responders ($n = 189$) decreased from 3.5±2.2 to 1.5±1.5 and rescue medication decreased from 0.9±0.6 to 0.6±0.9 at the end of the run-in phase. PI for the nonresponders to BUP TDS treatment remained almost unchanged (from 4.3±2.6 to 4.1±2.0), and the consumption of rescue medication even increased (from 2.0±2.7 to 2.7±2.0) over the run-in phase. For the 94 patients allocated to BUP TDS treatment, PI remained at 1.5±1.5 until the end of the maintenance phase, with a stable intake of BUP SL (1.0±1.0 tablets). By contrast, for the 94 patients allocated to placebo treatment, PI increased from 1.5±1.5 to 2.7±1.9 and the intake of BUP SL increased from 0.6±0.9 to 1.7±1.4 tablets over the maintenance phase (Fig. 2). The differences in baseline-corrected pain intensity and rescue medication between treatment groups at the end of the two-week maintenance phase were 0.91±0.22 points ($P < 0.0001$) and 0.52±0.20 tablets ($P < 0.01$) (Table 2), respectively.

### Side Effects

The most commonly reported adverse events during the study were nausea, vomiting, and constipation (Table 3). The majority of adverse events were mild or moderate in severity. A total of 44 serious adverse events were reported during the study, but only two serious adverse events (nausea, vomiting) in one patient were considered to be probably related to BUP TDS. Eleven patients died during the study, eight during the run-in phase, and three (one BUP TDS, two placebo) during the maintenance phase. None of the deaths was related to the active study medication.

### Global Satisfaction with Treatment

Most patients rated their global satisfaction with BUP TDS treatment as excellent, very good, or good. In the placebo group, most patients gave satisfaction ratings of very good, good, or poor (Table 4).

### Discussion

The European Medicines Agency (EMEA) guidelines on chronic pain recommend comparison of active treatment versus placebo.
to prove efficacy. In cancer, it is difficult to expose patients to placebo to prove the efficacy of analgesic methods, owing to ethical constraints. In addition, cancer is frequently progressive and this results in methodological limitations to pain assessments.

This study is the largest placebo-controlled study ever performed in patients with cancer pain. Therapeutic equivalence trials in cancer pain have limitations, mainly owing to the high number of patients needed to prove efficacy. An enriched design, as used in this trial, allowed a reduced number of patients because the effect size was higher, and a shorter placebo exposure compared to a conventional parallel design. Although selecting patients in an enrichment phase might raise concerns about the generalizability of results, the response to opioids is normally high and seems to be a continuum dependent upon dose escalation and limited by the occurrence of intolerable side effects; any selection bias, therefore, may be of minor importance. The good response to cancer pain treatment with strong opioids is well established and has repeatedly been shown to be in the range of 70% by use of the analgesic ladder. Indeed, the enrolled patients who had been pretreated with opioids at inclusion showed a high rate of satisfactory pain relief (70%) at the end of the run-in phase. Furthermore, the enrichment approach reflects clinical practice, which is to start
opioid treatment and assess the patient’s responsiveness by dose adjustment. The use of sublingual BUP as rescue medication in this study allowed more effective pain management as well as being ethically sound for patients receiving the placebo patch.

Patients’ enrollment was left to the investigator’s decision and was based on an estimated opioid requirement of 90 mg/d or more of oral morphine, as well as an inability to increase the previous opioid despite inadequate pain relief because of the risk of intolerable side effects. The need for an increase in the dosage adequately reflected severe pain intensity. Most tramadol pretreated patients received combination therapy with strong opioids, which accounts for the relatively low dose range of 400–600 mg tramadol. It also reflects the lower potency of the substance, which resulted in the need to switch to a strong opioid in these cases of advanced cancer.

During the run-in period, the mean daily pain intensity and the mean daily intake of rescue medication both decreased in 70% of patients in the first 12 hours following patch application, indicating a good response to BUP TDS. This may explain the PI levels of 3.5 in the initial phase of treatment, which
would have been far higher if a washout phase had been implemented. Patients could not be washed out from previous opioids for ethical reasons, so the first pain assessment took place under BUP TDS treatment. Among patients not responding to BUP TDS, the mean daily pain intensity decreased only slightly and the mean intake of rescue medication increased. This lack of response may reflect disease progression or undertreatment at the patch dosage of 70 μg/h. Owing to the study design, the patch dosage could not be further increased beyond 70 μg/h despite being labeled for the use of up to 140 μg/h.

For the primary efficacy endpoint of overall response during the maintenance phase, significantly more patients in the BUP TDS group than the placebo group were responders. The two-point reduction of pain intensity in the BUP TDS group, from the start of the run-in phase to the end of the maintenance phase, corresponds to clinically important changes reported by others. In the placebo group, the reduction of pain intensity in the run-in phase followed by an increase of pain intensity in the maintenance phase validates the results. These could otherwise be criticized for evaluating efficacy in a placebo group supplemented by sublingual BUP.

There was a good relation between reduction of pain in the BUP TDS group and global satisfaction with treatment as an indicator of clinically important benefit. As expected for a study design in which active treatment was withdrawn, patients receiving placebo remained on treatment for a shorter period, whereas their mean pain intensity and consumption of rescue medication both increased. This produced a difference in baseline-corrected pain intensity between treatment groups of almost one point, and a concomitant difference in rescue medication intake of 0.5 tablets. Global satisfaction with treatment was rated as "poor" by more placebo patients than BUP TDS patients, but a high percentage rated it "very good" or "good," reflecting the large proportion of placebo responders.

The high placebo response observed in this study is a typical phenomenon often reported by analgesic studies. The subjective nature of patient ratings, with high interindividual variability, multifactorial influences on pain perception, and cognitive and conditioning mechanisms, may alone provoke a response. In view of the high placebo effect of the patch itself, the observed difference in pain intensity of one point between treatments is even more clinically relevant.

The reduced incidence of adverse events observed in the maintenance phase reflects the process of selecting only patients responding to treatment. In contrast to plasma fluctuations induced by immediate release oral formulations, TDS formulations are expected to reduce adverse events by slowly releasing the drug into the bloodstream and maintaining a steady plasma concentration. Reduced side effects, especially for constipation, were repeatedly reported for transdermal systems and may be related to a bypass of enteral opioid receptors. The constipation rate of 7.4% was comparable to previous results with BUP TDS, and lower than fentanyl TDS or sustained-release morphine, which produce constipation rates between 20% and 44.5%. Nausea and vomiting were more frequent in placebo patients, possibly owing to a higher intake of fast-acting sublingual

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rescue medication, or to the discontinuation of BUP TDS producing early withdrawal symptoms. As the elimination of active compound following patch removal is slow, and unlimited rescue medication was available, the symptoms were of at least mild intensity. Given the small difference in adverse events between groups, as well as the high proportion of placebo responders, an unblinding of patients who were possibly suffering from early withdrawal symptoms, or with an increased intake of rescue medication, was unlikely.

In conclusion, we believe that the enriched study design is a valid approach, as the selection bias was relatively low for a symptomatic pain-relieving treatment modality. Substitution of analgesic therapy by unlimited immediate-release rescue opioid in the placebo group is ethically acceptable, especially in view of the low withdrawal rate. The superiority of BUP TDS (70 μg/h) to placebo is an important outcome supporting an evidence-based treatment rationale. Additionally, the reported side effects demonstrate that BUP TDS had a good safety profile. BUP TDS at a dose of 70 μg/h can, therefore, be considered an effective and well-tolerated option for the management of severe cancer pain. Nevertheless, inclusion of an active comparator group, for example, morphine, should be considered for subsequent studies.

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