ORIGINAL ARTICLE

Opioid Rotation from High-Dose Morphine to Transdermal Buprenorphine (Transtec®) in Chronic Pain Patients

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Abstract: Opioid rotation is increasingly becoming an option to improve pain management especially in long-term treatment. Because of insufficient analgesia and intolerable side effects, a total of 42 patients (23 male, 19 female; mean age 64.1 years) suffering from severe musculoskeletal (64%), cancer (21%) or neuropathic (19%) pain were converted from high-dose morphine (120 to >240 mg/day) to transdermal buprenorphine. The dose of buprenorphine necessary for conversion (at least 52.5 µg/h) was titrated individually by the treating physician. No conversion recommendations were given and the treating physician used his or her own judgment for dose adjustment. Pain relief, overall satisfaction and quality of sleep (very good, good, satisfactory, poor, or very poor), and the incidence and severity of adverse drug reactions over a period of at least 10 weeks and up to 1 year was assessed. Following rotation, patients experiencing good/very good pain relief increased from 5% to 76% (P < 0.001). Only 5% reported insufficient relief. Relief was achieved with buprenorphine alone in 77.4%, while 17% needed an additional opioid for breakthrough pain. Sleep quality (good/very good) increased from 14% to 74% (P < 0.005). Adverse effects were reported in 11.9%, mostly because of local irritation, did not result in termination of therapy. Neither tolerance nor refractory effect following rotation from morphine to buprenorphine was noted. Conversion tables with a fixed conversion ratio are of limited value in patients treated with high-dose morphine.

Key Words: transdermal buprenorphine, morphine, opioid rotation, chronic pain, cancer pain

INTRODUCTION

Persistent pain of moderate to severe intensity is an indication for the use of potent opioids step III of the World Health Organization (WHO) ladder in pain. Morphine is the reference agent for step III opioids. Morphine, however, like any opioid, is not free of side effects. Clinical experience, especially in long-term therapy, has shown that patients achieve adequate analgesia with morphine, but a significant number suffer from intolerable side effects, inadequate pain relief, or both. Side effects include nausea, vomiting, dizziness, fatigue, constipation, itching, and respiratory depres-
sion. Other opioid-related effects, such as addiction, dependence, and analgesic tolerance, are concerns when administered for long-term management. When the dose has to be progressively increased an alternative agent might be considered. Compared to sustained-release morphine, transdermal buprenorphine presents an attractive option as it has similar efficacy with respect to analgesia, and patients receiving buprenorphine have been reported to experience fewer side effects. Moreover, changing to another opioid, known as “opioid conversion” or “opioid rotation,” is an effective strategy to improve analgesia, reduce persistent side effects, and reduce toxicity and/or tolerance. Switching patients to an alternative opioid is increasingly becoming an option to avoid adverse effects in cancer pain, and in noncancer pain. For some patients this may be the only viable option to reestablish sufficient pain relief. Thus, for opioid-related side effects or for inadequate pain relief, the WHO guidelines for managing cancer pain recommend the rotation to another opioid and/or a different route of administration. Importantly, one reason for switching is opioid dose escalation, which cannot be explained by the underlying disease of the patient.

Buprenorphine is a potent opioid suitable for patients requiring intense analgesia. Pharmacologically, buprenorphine is characterized as a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor. Previously available in parenteral and sublingual formulations, buprenorphine can now be administered using a transdermal delivery system (Transtec®; Gruenethal GmbH, Aachen, Germany). The active agent is embedded in an adhesive polymer matrix, providing continuous and steady release of the compound for long-term use. The buprenorphine patch is commercially available in three different release 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.

In order to evaluate the potential use of the partial agonist for rotation in patients on high-dose morphine with insufficient pain relief, we evaluated 42 patients who were switched from morphine to transdermal buprenorphine. The rationale for the rotation to buprenorphine is its purported interaction with a different subset of G-proteins, which results in less tolerance to the analgesic effect compared to morphine. When rotating from one opioid to another, conversion tables are often used. While these tables propose a fixed conversion ratio for equipotent doses of two different opioids for various routes of administration (eg, oral, parenteral, transdermal), caution should be exercised, especially in patients receiving high doses. Sittl et al. demonstrated transdermal buprenorphine to be more potent in patients receiving chronic opioid treatment than expected based upon the conversion table provided in the label. We undertook this analysis to determine the feasibility of switching high-dose morphine to transdermal buprenorphine in a “real world” setting.

METHODS

In a prospective open-label, post marketing surveillance study, performed in compliance with current human subject guidelines, data were obtained from 42 patients taking >120 mg of oral morphine. Patients were treated in general practice, in hospitals and in pain clinics for pain of different origin. The objectives for switching from high-dose morphine to a buprenorphine patch were either inadequate pain relief as reported by the patient (visual analog scale >5.0) or severe side effects. The dose of buprenorphine necessary for conversion (at least 52.5 µg/h) was titrated individually by the treating physician. No conversion recommendations were given and the treating physician used his or her own judgment for dose adjustment.

Demographic data, medical history, comorbidities, the cause of pain, current pain therapy, and the use of adjuvant therapy prior to enrollment as well as pain relief and quality of sleep were determined by the treating physician. In addition to reasons for rotation, the dosages necessary for sufficient pain relief during rotation as well as the necessary adjuvant following rotation were recorded. Also, the type and severity of side effects as well as reasons for possible termination of transdermal buprenorphine therapy during the study period were collected for at least 10 weeks, and in some cases up to 1 year.

For the evaluation of efficacy of rotation, endpoints of pain relief and quality of sleep were rated by a physician using a 5-point scale: 0 = very good, 1 = good, 2 = satisfactory, 3 = weak, 4 = no pain relief. For the assessment of quality of sleep, the following verbal rating scale was used: 0 = very good, 1 = good, 2 = satisfactory, 3 = poor, 4 = very poor.

Statistical Analysis

Mean pain severity and mean sleep impairment before and after switching were evaluated. To demonstrate differences in pain relief and quality of sleep before and after rotation, Friedmann analysis of variance followed
by Dunn’s multiple comparison test was used. A value of $P < 0.05$ was considered significant.

**RESULTS**

A total of 42 patients were included in the analysis with 23 (54.8%) males and 19 (45.2%) females (Table 1). The daily morphine dose was used to divide patients into three groups for evaluation. Group I ($n = 14$) received 120 mg/day, group II ($n = 13$) needed 121–240 mg/day, and group III ($n = 15$) required >240 mg/day of oral morphine. Group III included patients with doses up to 800 mg/day with a mean >400 mg/day. The majority of patients in Groups II and I were male (60%), while the genders were equally represented in Group III (Table 1). The mean age of all patients was 64 years, with a range of 34 to 86 years.

Major reasons for opioid therapy in the study population included musculoskeletal pain in 27 patients (64%), cancer pain nine patients (21%) with six (14%) having metastases, and neuropathic pain in eight subjects (19%). The major reason for rotation to transdermal buprenorphine was insufficient analgesia in 37 patients (88%). In 23.8% severe side effects (e.g., nausea, emesis, sedation, dizziness) were the reason for rotation and in 19% insufficient compliance was considered a reason for the switch from oral morphine to a transdermal patch. Finally, one patient (2%) was adjusted to buprenorphine because of renal impairment (Figure 1).

Two-thirds of the patients (67%) had received morphine for more than 6 months. In nearly one-third (29%) the duration of morphine treatment prior to the buprenorphine switch was 1 to 6 months. Two patients received morphine for less than 4 weeks. Following rotation from high-dose morphine to transdermal buprenorphine, there was a significant improvement in pain. During treatment with high-dose morphine, only 5% of all patients had good to very good pain relief. This percentage increased significantly to 76% following the rotation to transdermal buprenorphine ($P < 0.005$). The percentage of patients with a poor to satisfactory pain relief during morphine therapy decreased from 95% to 17% following the switch to transdermal buprenorphine ($P < 0.001$). A beneficial effect on pain relief after rotation to transdermal buprenorphine was also observed in the smaller subset of patients followed for more than 12 months. These patients, initially reporting very good to good pain relief, stayed on a stable analgesic dose over this longer observation period (Figure 2).

### Table 1. Demographic Data of Patients Rotating from High-Dose Morphine to Transdermal Buprenorphine

<table>
<thead>
<tr>
<th>Oral Morphine Dose (mg/day)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 14</td>
<td>120</td>
<td>121–240</td>
<td>241–800</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.6</td>
<td>65.2</td>
<td>69.8</td>
</tr>
<tr>
<td>[min-max]</td>
<td>[49–79]</td>
<td>[51–86]</td>
<td>[34–80]</td>
</tr>
<tr>
<td>Gender Male/female</td>
<td>8/6</td>
<td>8/5</td>
<td>7/8</td>
</tr>
</tbody>
</table>

**Figure 1.** Reasons for rotating from high-dose morphine to transdermal buprenorphine.

**Figure 2.** Pain relief scores.
Using the 5-point evaluation scale at the beginning and end of the rotation period, assessment of quality of sleep demonstrated significant improvement. While sleep quality before rotation was rated as very poor to poor or satisfactory in 86% of the study sample (36 patients), by the end of the observation period 74% (31) of patients assessed their sleep quality as very good to good, and only 12% (5 patients) rated their sleep as satisfactory ($P > 0.005$). Two patients judged their quality of sleep as poor and an additional two judged their sleep as very poor following the switch to buprenorphine (Figure 3). Overall, improvement in quality of sleep was seen in 74% of the total study population (31 patients), while 21% (nine patients) reported no change, and in two patients quality of sleep had deteriorated. Thus, switching from high-dose morphine to transdermal buprenorphine resulted in a reduction of impairment of sleep quality by a median of 45% in at least half of the study population.

The dosages necessary to rotate from morphine to transdermal buprenorphine differed significantly in the three morphine groups. One patient used less than 52.5 µg/h, 29 patients (69%) needed a 52.5 µg/h transdermal buprenorphine patch, 11 patients (26%) started off with 70 µg/h, and one patient started off with a dose of 105 µg/h. As the largest commercially available patch is 70 µg/h, higher doses were achieved by applying more than one patch. It should be noted that there was not a close relationship noted between the patch size necessary for sufficient pain relief and the dose of morphine taken previously. In general, the dose of buprenorphine required for sufficient pain relief was comparatively low considering dose of morphine taken before the switch (Table 2). Although 120 mg of oral morphine is considered equipotent to 70 µg/h of transdermal buprenorphine in standard practice, the initial buprenorphine dose necessary for sufficient pain relief was much lower.

In addition, the dose necessary for pain relief showed little increase throughout the observation period (Table 2 and Figure 4). While a total of 30 patients (71%) remained on their initial dose, two patients reduced their required dose and remained on the lower level until the end of the study period. In 10 patients (24%) the starting dose of transdermal buprenorphine had to be increased to the next larger patch size, which then remained stable at the higher level.

Prior to the rotation 16 out of 42 patients needed a laxative, nine patients took an NSAID (non-steroidal anti-inflammatory drug), three an antidepressive agent, and one patient took a steroid as a coanalgesic. Follow-

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**Table 2. Dosages of Transdermal Buprenorphine**

<table>
<thead>
<tr>
<th>Morphine Group, Dose (mg)</th>
<th>Start of Study: Patients (N) in Each Dose Category—Transdermal Buprenorphine (µg/h)</th>
<th>End of Study: Patients (N) in Each Dose Category—Transdermal Buprenorphine (µg/h)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: 120</td>
<td>$&lt;52.5$  8  5  0</td>
<td>$&lt;52.5$  6  7  1</td>
<td>14</td>
</tr>
<tr>
<td>II: 121–240</td>
<td>0  11  1  1</td>
<td>1  9  2  1</td>
<td>13</td>
</tr>
<tr>
<td>III: 241–800</td>
<td>0  10  5  0</td>
<td>0  8  5  2</td>
<td>15</td>
</tr>
</tbody>
</table>
ing the switch, the number of patients requiring a laxative dropped to one ($P < 0.001$), 13 patients were given an antidepressive, 16 took an additional NSAID, and three an antiepileptic agent for adjuvant pain therapy. It should be noted that during the observation period, 71.4% of the total 42 patients were sufficiently treated with a sole transdermal buprenorphine patch, and only seven patients were in need of an additional opioid of the WHO Step III ladder (one oxycodone, one sublingual buprenorphine, five oral morphine preparation) for the relief of breakthrough pain.

The side effects after the switch related to the transdermal patch were local skin reactions (11.9%) and, in one patient (2.4%), hyperhidrosis. No additional serious adverse events were observed after rotation to transdermal buprenorphine and none of the side effects resulted in withdrawal from study or discontinuation of therapy.

**DISCUSSION**

To our knowledge, these are the first published results in patients on high-dose morphine rotated to transdermal buprenorphine. This study has limitations, including the lack of a comparative or placebo group, which may result in a possible overestimation of the analgesic effect of the new agent. The study, however, has the advantage of reflecting current medical practice in a realistic setting. While this was not a controlled study, the data presented are clinically relevant as they were collected during a prospective open-label design.

Despite the use of high doses of morphine, in a clinical setting certain patients demonstrate insufficient pain relief or exhibit a high incidence of morphine-related side effects making rotation necessary. In this study insufficient pain relief was the reason for rotation to buprenorphine in two-thirds of patients. Although an increase in the underlying disease in cancer patients is often the cause for escalation of morphine dose, the development of tolerance to the opioid also must be considered. The majority of patients (64%) in this study took the opioid for treatment of musculoskeletal pain. Long-term use of high-dose morphine can lead to an increase in side effects in part because of two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide. An accumulation of M3G correlates with an increase in side effects, central nervous system symptoms, and an “antiopioid” effect that may contribute to the development of tolerance. Our data support such supposition as switching to another opioid resulted in an increase in pain relief and a reduction in the incidence of side effects. Therefore, rotation presents a valuable option with the potential to improve the quality of life.

In this context, the present data demonstrate that rotation from high-dose morphine to transdermal buprenorphine might be an effective option in the step III of the WHO ladder. Buprenorphine was, in this study, a viable alternative to morphine therapy with substantial benefit in both analgesia and sleep quality.
following opioid rotation. The increase in analgesic efficacy over morphine and the high percentage of patients who used buprenorphine as the sole opioid (80%) after rotation might be attributed to buprenorphine’s ability to activate a subgroup of the G-protein class, purportedly resulting in a reduced potential for the development of tolerance.18

In the majority of cases (71%), the dose of transdermal buprenorphine for sufficient pain relief after rotation was 52.5 µg/h with a smaller number of patients receiving 70 µg/h. These doses are much lower than anticipated according to currently used conversion tables where the equipotent ratio of oral morphine to transdermal buprenorphine is 75:1.25 From the present data, it can be deduced that conventional conversion tables are of limited clinical use.7,26,27 In fact, a recent retrospective study reckoned that the appropriate equipotent ratio of morphine to transdermal buprenorphine is 110:1 or even 115:1.25 Although more clinical data are required to make definitive recommendations, these results corroborate the higher potency of transdermal buprenorphine in this setting. In contrast to the proposed conversion rate from morphine to transdermal buprenorphine of 100:1 as originally suggested by Sittl et al.,19 our data imply the equianalgesic doses be adjusted by approximately 30%. It is therefore suggested that the physician should only use conversion tables as a rough guide, because these scales may tend to overestimate the dose of the new opioid.24 In this context is also interesting to note that the dose in patients with previous high morphine consumption did not correlate with the required dose of transdermal buprenorphine for sufficient pain relief. Such data support the perception that a narcotic analgesic converter is only useful in the sense of being an approximate guide when switching to another opioid and support the notion that conversion scales should not be translated directly into practice.7,28,29

In regard to opioid conversion, the present results indicate that a reliable conversion calculator for finding the proper equianalgesic dose for use with opioid rotation does not exist. Appropriate opioid conversion in patients is a process requiring in-depth understanding of complex pharmacologic issues. The type of pain being treated, its time course, and previous treatment all contribute to the need for individual dose titration. This may be especially important when patients are using more than 120 mg morphine before rotation (groups II and III), where the potential development of tolerance must be considered.

The consistency in buprenorhine dosages necessary to maintain pain relief suggests a lower incidence of tolerance development. As rotation to transdermal buprenorphine was not followed by dose escalation during the observation period of up to 1 year, stability of dosages seemed in this study to be a specific trait of buprenorphine. Although the necessary dose of buprenorphine had to be increased in the 10 cancer patients, this could also be attributed to an increase in the underlying disease.

In addition to the apparent reduced development of tolerance, in comparison to high-dose morphine, side effects with transdermal buprenorphine, especially constipation, were reduced. No serious adverse events were noted. Also, rotation from high-dose morphine to buprenorphine, together with concomitant dose adjustment, was accomplished without any instance of withdrawal symptoms from morphine. Thus, the physician in routine clinical practice can easily handle conversion from oral morphine to transdermal buprenorphine.

Additional limitations of this study, the small sample size and the diversity of pain syndromes included, are acknowledged. Nonetheless, the striking benefit patients achieved from rotation in this clinically relevant setting suggests conversion from high-dose morphine to buprenorphine is worthy of consideration when insufficient pain relief and/or intolerable side effects present during morphine therapy.

In summary, the present data support the notion that switching from high-dose morphine to transdermal buprenorphine is feasible. Patients demonstrated a significant improvement in analgesia while at the same time benefiting from an enhancement in their quality of sleep. In addition, as conventional conversion tables may be misleading, they should only be used as a rough guide for dose adjustment: typically starting with a lower than calculated dose, increasing the dose as necessary. While rotation from oral morphine to transdermal buprenorphine resulted in a higher incidence of pain relief, following stabilization, in the majority of cases the dose remained constant.

REFERENCES


