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Survey on the use of buprenorphine patches in the palliative care practice

Abstract

Transdermal buprenorphine is a new formulation of the old drug available for the treatment of cancer and non-cancer pain. The drug offers number of interesting new features and was found effective in clinical trials in cancer patients with pain. We performed a survey of the use of buprenorphine patches for one year. In the survey we included 58 admitted patients (67 admission periods), whose clinical records and drug charts were subjected to analysis. Opioid naive patients were started either on 5 or 10 μg/hour. Mean buprenorphine dose was 22.3 μg/hour (95% CI: 16–28.6), increased on day 8 to 25.4 μg/hour (95% CI: 18.6–32) and ended up at the dose of 31.3 μg/hour (95% CI: 20.9–41.6) on the last day of treatment; day 19 (95% CI: 14.5–23.5). The overall dose increase was approximately 2% per day. Approximately half of the patients needed beside buprenorphine other opioids either in a slow release or immediate release form, usually morphine or oxycodone. Swapping from morphine, oxycodone and fentanyl to buprenorphine was without problems in all of the cases. The doses of all opioids administered calculated as oral morphine equivalents showed insignificant decreases for morphine and oxycodone to buprenorphine swaps. In case of fentanyl the oral morphine equivalents of opioids were significantly lower after swap ($p = 0.0039$). No signs of antagonism between the drugs were observed. In conclusion: buprenorphine patches appear to be useful in the treatment of cancer pain, either as monotherapy or in combination with other opioids. Swap from fentanyl to buprenorphine offers perspective of achievement of pain control with much less toxicity and should be investigated in more detail.

Key words: buprenorphine, palliative care, cancer pain, opioids switching

Adv. Pall. Med. 2010; 9, 2: 39–44

Introduction

Opioids remain the mainstay of the treatment in cancer pain [1, 2]. There are many opioids available on the market and it is unclear which one should be used when. It is also impossible to say which opioid is better than the other and the choices are made randomly basing on their availability, price and the patient friendliness. Biased articles, not based on any experience, commissioned by the pharmaceutical industry have potentially high impact on prescribing [3]. The simple notion that pure or full μ-opioid-receptor agonists are better than partial agonist was never proven in clinical trials and buprenorphine was underused for many decades.

Buprenorphine sublingual tablets are known in pain control for several decades [4]. The drug was found effective in cancer pain in settings rel-

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Advances in Palliative Medicine 2010, 9, 39–44

evant to palliative care [4–10]. Newly formulated transdermal buprenorphine patches was reintroduced recently and apparently possess some interesting features which may be used to the benefit of patients with pain. The data on the use of this new formulation are still limited. There is not much experience in switching to buprenorphine from other opioids and this stimulated us to perform this survey. Also, it was important to observe how much of the other opioids need to be given together with buprenorphine to obtain optimal effect.

Material and methods

Drug charts were analysed retrospectively from 01.04.2009 until 01.04.2010. All patients with completed admission resulting either in discharge or death were included into survey. Patients treated in the out-patient clinic were excluded from this survey as exact data on the use of breakthrough medication was usually missing. Some patients were admitted more than once and the separate admissions of the same patients were included in some analyses. Patients were admitted to the ward and their pain was assessed. When the pain was inadequately controlled and/or the therapy with opioids caused unacceptable adverse effects, the patients were swapped from the original opioid to buprenorphine. For calculation of the doses of opioids opioid calculator was used from the website: http://book.pallcare.info/index.php?op=plugin&src=opiconv. The initial dose of buprenorphine when swapped from fentanyl was decreased by 50% in comparison to the calculated dose (μg/μg). The doses of buprenorphine were adjusted after one week in order to obtain optimal results. For the analysis, usually the dose of drugs on day 8 was taken for analysis, as well as the last full day of treatment before either death or discharge. For analysis all opioids were converted into oral morphine equivalents (OME) per 24 hours. Dose increments of buprenorphine were calculated as percentage of the original dose per day. Probability was calculated with the Wilcoxon exact test and values of $p < 0.05$ were considered significant.

Results

Patient's demographics

In the period of 12 months 289 new patients were admitted to the Dove House Hospice. Fifty eight new patients (20%) were prescribed buprenorphine. Six patients were admitted more than once, hence 9 admission periods were added to the survey, making total numbers of admission periods equal 67. Forty seven (81%) patients prescribed buprenorphine were suffering from cancer, of which 14 (30%) was lung cancer. The mean age of all patients was 67 (95% CI: 45–84). There were 36 women (62%) and 22 men (38%). Mean admission duration was 18 (95% CI: 14.9–21.2) days while mean number of days when patients were treated with buprenorphine was 15.8 (95% CI: 12.7–18.8). Some patients were started on buprenorphine after a couple of days of observation. Total number of treatment days was 1071. Forty two treatment periods (62%) ended up with discharge, 24 (35%) with patient's death and in 2 cases (3%) the treatment was discontinued because of adverse effects.

Starting dose of buprenorphine and dose increments

Eleven patients who were opioid naive started on 5 μg/hour (9 patients) and 10 μg/hour (2 patients). In this group the initial dose remained the same until the end of the observation period suggesting good pain control. In this group only occasionally other opioids were used. In 36 patients buprenorphine was initiated by us and the duration of this admission period was longer than 7 days. Shorter admission periods were not analysed. In these 36 patients mean initial dose of buprenorphine was 22.3 (95% CI: 16–28.6) μg/hour and increased on day 8 to 25.4 (95% CI: 18.6–32) μg/hour and ended up at the dose of 31.3 (95% CI: 20.9–41.6) μg/hour on the last day 19 (95% CI: 14.5–23.5). The overall calculated dose increase was approximately 2% per day. There was no significant difference in dose increase percentage between the titration phase (day 1–7) and the following treatment days.

Time to the optimal dose

Time to establish the optimal dose was estimated in 47 patients who started with buprenorphine during the first admission. In 25 patients (53.2%) the initial dose was immediately the optimal dose and was not adjusted during the rest of the treatment period. In 11 patients (23.4%) the optimal dose was established within 8 days and continued thereafter, in 5 patients (10.6%) the optimal dose was established between 7–14 days and in 6 patients (12.8%) cases the dose was established in more than 15 days or could not be established at all and was still rising. This included patients whose dose of buprenorphine increased in the last week of life. It is probable that many patients with rising doses of buprenorphine and other opioids at the end of their lives had increase of pain intensity and/or developed opioid tolerance.

Swapping to buprenorphine

From 49 patients initiated by us on buprenorphine, 11 (22.4%) were previously opioid naive, 10 (20.4%) were on oxycodone, 12 (24.5%) were on morphine sulphate, 4 (8.2%) on fentanyl, 4 (8.2%) on morphine and fentanyl, 2 (4%) on oxycodone and fentanyl, 2(4%) on morphine, s.c. diamorphine and fentanyl, 1 (2%) on morphine and s.c. diamorphine and 3 (6%) on codeine.

Swapping to buprenorphine from oxycodone and morphine

Ten patients were swapped from oxycodone to buprenorphine (Figure 1). In most cases because of insufficient pain control. The dose of oxycodone (in OME) prior to swap was 177.5 mg/24 hours (95% CI: 23–332). The dose of buprenorphine and oxycodone on day 8 was 193.8 mg/24 hours (95% CI: 21.3–408.8) in OME and at the last day — 20 (95% CI: 3.9–36) the dose of buprenorphine and oxycodone was 140.9 (95% CI: 4–277.8). The differences of the means were not statistically significant (p = 0.3)

In 6 cases the swap resulted in final lower doses of buprenorphine or no need of other opioid medication at all. In 4 cases the swap resulted in only minimal or no decrease of the dose and the patients still needed considerable doses of other opioids. In none of the cases final dose of opioids was higher than the original dose before swap.

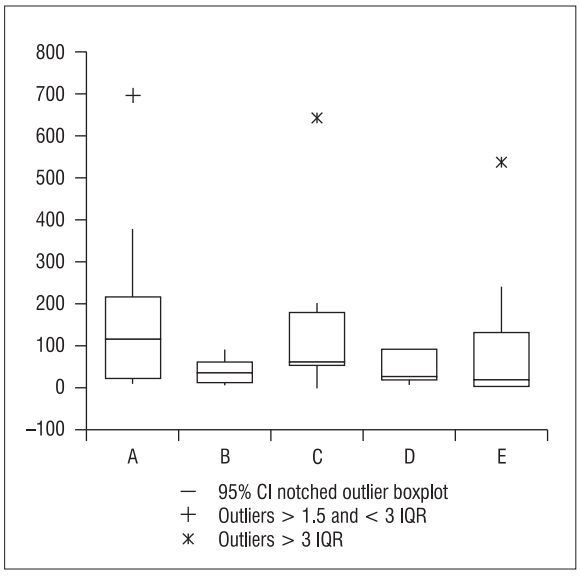

Figure 1. Swap of oxycodone to buprenorphine (n = 10). On the Y axis, oral morphine equivalents in mg/24 h. A — oxycodone dose prior to swap, B — buprenorphine dose on day 8, C — dose of oxycodone on day 8 still needed to provide good pain control, D — dose buprenorphine on the last day of treatment, which was day 20 (95% CI: 3.9–36), E — dose of oxycodone on the last day of treatment still needed to control pain. The differences between the groups were not significant (p = 0.3)

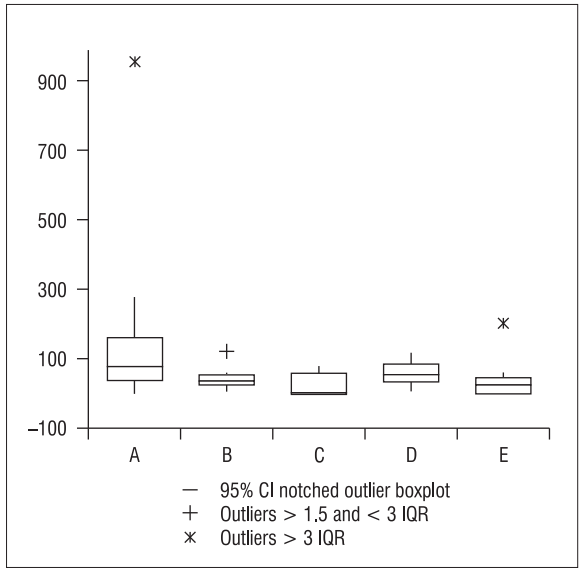

Figure 2. Swap of morphine sulphate to buprenorphine (n = 12). On the Y axis, oral morphine equivalents in mg/24 h. A — morphine dose prior to swap, B — buprenorphine dose 8 days after swap, C — dose of morphine on day 8 still needed to maintain pain control, D — buprenorphine dose at the last day of treatment: day 13 (7.1–18.4), E — dose of morphine still needed to maintain analgesia. The differences between the groups were not significant (p = 0.3)

Twelve patients were swapped from morphine sulphate to buprenorphine (Figure 2). The dose of morphine prior to swap was 162.7 mg/24 hours (95% CI: 4.5–329.9) in OME. On day 8 the dose of buprenorphine and morphine was 71.6 mg/24 hours (95% CI: 20.1–123) and on the last day of the treatment; day 13 (7.1 to 18.4), the dose of buprenorphine and morphine was 97.5 mg/24 hours (95% CI: 44.1–150.9). The differences between these means were not statistically significant (p = 0.3). In 8 cases the swap resulted in final, much lower doses of buprenorphine or no need of other opioid medication at all. In 4 cases the swap resulted in only minimal or no decrease of the dose and the patients still needed considerable doses of other opioids. In none of the cases final dose of opioids was higher than the original dose before swap.

Swapping to buprenorphine from fentanyl

Twelve patients were swapped from fentanyl to buprenorphine (Figure 3). Ten because of in-

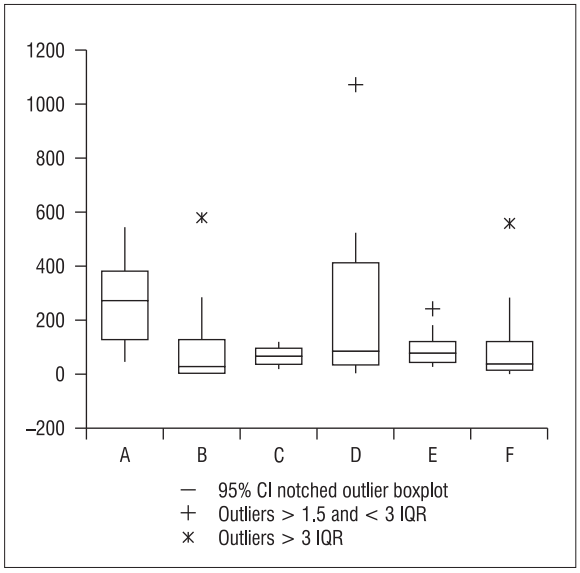

Figure 3. Swap of fentanyl to buprenorphine (n = 12). On the Y axis, oral morphine equivalents in mg/24 h. A — fentanyl dose prior to swap, B — dose of other opioids needed to control pain, C — dose of buprenorphine on day 8, D — dose of other opioids on day 8, E — dose of buprenorphine in the last full day of treatment which was day 18 (95% CI: 11–24.1), F — dose of other opioids in the last full day of treatment. The differences between A and C, A and E were statistically significant (p = 0.0039)

adequate pain control, two because of adverse effects. Only 4 patients were on fentanyl alone. Other needed other opioids prior to swap. When doses of opioids were converted to OME prior to swap, the dose of fentanyl and other opioids was equal to 368.2 mg/24 hours (95% CI: 185.8–550.6). On day 8 after swap the dose of buprenorphine and other opioids was equal to 309.9 mg/24 hour (95% CI: 53–566.7). At the last day of treatment; day 18 (95% CI: 11–24.1), the dose of buprenorphine and other opioids was 196.4 mg/24 hours (95% CI: 60.3–332.6). The difference in the doses of opioids between day 0 and the last day of treatment was statistically significant (p = 0.0039).

Figure 3 shows fentanyl and other opioids (in OME) on day 0, day 8 of the treatment and on the last day of the treatment. While on day 0 the dose of fentanyl was high and the dose of other opioids low, this changed on day 8. Lower doses of buprenorphine were matched by higher doses of other opioids. On the last day of treatment the dose of buprenorphine remained approximately the same, but the dose of other opioids decreased to the level comparable to day 0.

Table 1. Adverse effects in patients treated with buprenorphine

Adverse effect	Number of patients
Confusion	2
Hallucinations	1
Nausea	1
Drowsiness	2
Skin irritation	1
Adhesion problems	1

Adverse effects

Eight of the 58 (13.8%) patients treated with transdermal buprenorphine experienced intolerable adverse effects (Table 1). One patient experienced hallucinations four days after beginning of the treatment. This prompted us to discontinue buprenorphine. One patient was claimed by the family to be confused after one day of treatment with 5 μg/hour. Family requested to discontinue treatment. One patient who was slightly confused was successfully treated with haloperidol. For the other seven, the symptoms began hours to days after increasing the dose and reducing the dose resulted in the symptoms settling down and in all cases disappearing. Several patients developed skin rash under the patch. In no one case this was the reason to discontinue treatment. However, data on the skin rash were not well reported in the notes. The same is true for the constipation. Many patients were constipated and were treated with laxatives. This adverse effect was never intolerable and did not influence changes of medication. Several patients treated with other opioids prior to begin with buprenorphine were intolerably constipated and this symptom became less pronounced after swapping to buprenorphine. No rebound diarrhoea was observed. Unfortunately this too was not well reported in the notes and cannot be analysed here.

Discussion

Transdermal buprenorphine is available since short for the treatment of cancer and non-cancer pain. It is still not trusted and is grossly underused simply because of ill funded notion that pure opioid agonists would be better than partial agonists [3]. In our hospice we performed a survey of the use of this drug and its potential value in cancer pain control. The value of the data presented by us is limited by the retrospective character of our survey, low number of patients in each group and impossibility to take into account other than opioid treatments like

use of steroid injections, use of NSAIDs, paracetamol and radiotherapy. The survey did not analyse directly the pain intensity reported by the patient, but only the use of other, usually PRN opioids as a surrogate for this. These data are indirect, but still mirror everyday practice.

Main goal of the survey was to establish safe initial doses of buprenorphine patches in old and frail terminally ill patients, possible problems of combining opioids like morphine and oxycodone, the dose of additional opioids needed to obtain analgesia, possible antagonisms and the problems with switching from one opioid to the other.

Buprenorphine had been well tolerated by most of the patient. In many patients the doses of buprenorphine needed to control their pain were lower than of the original opioids or opioids combinations, which caused that many patients, after 1–2 days of treatment were much more alert and active.

Important finding is the fact that buprenorphine was generally used in low or very low doses. Especially initial doses of buprenorphine in naive patients were 5–10 μg/hour. Median dose of all buprenorphine prescribed to our patients was 20 μg/hour. In several countries, like Poland, buprenorphine's lowest dose is still 35 μg/hour and this patch should be changed every 4 days (Transtec®). In practice Transtec® patches were used only in 1/3 of the treatment periods studied by us. In 2/3s of the treatment periods the buprenorphine patches (Butrans®) were used in different combinations which should be changed once per week. This means that in countries where the Butrans® patches are still unavailable, the adequate treatment may be difficult or impossible. It is not advisable to cut the patches in pieces. And in fact in many countries this practice is banned.

The manufacturers' licence limits the use of the buprenorphine patches up to 140 μg/hour. This limitation puts many clinicians off as they think that this cap has something to do with the ceiling effect [11, 12] may limit their ability to increase the dose and finally they would need to swap back to other opioids which may then appear to be ineffective. In our survey only two patients needed the maximal dose of 140 μg/hour toward the end of their life. No signs of tolerance development or ceiling effect were observed in our patients. None of the patients needed to be swapped back to other opioid. The cap of 140 μg/hour is dictated probably by the intensity of exposure of the skin to the glue. Several patients developed in our survey a toxic effect to the glue (most probably not to the buprenorphine itself). Using high doses of patches means larger areas exposed to the glue toxicity and shorter rotation time of the site before the next patch is being administered. This may dramatically increase the frequency of local reactions. Beyond this survey, in a patient with osteoporosis, with good reaction to 140 μg/hour buprenorphine patches for 17 months and severe local reaction, we managed to swap the patient to the sublingual administration of buprenorphine, as previously all known opioids were found to cause unacceptable adverse effects.

Interestingly in half of the treatment periods patients were treated with buprenorphine only, and practically did not need any additional opioids, may be with the exceptions of the period just before death. In another half of the treatment periods, buprenorphine needed to be combined with other opioids. No signs of antagonism or loss of efficacy of the combinations was observed. Instead, in many patients, addition of buprenorphine made possible to use very low additional doses of other opioids. Equal good results were obtained in combination of buprenorphine with oxycodone as with morphine. The combinations of buprenorphine with fentanyl were avoided. In practice the efficacy of these combinations were equal, although not formally assessed as the numbers of patients in each group were rather small.

Swap from fentanyl to buprenorphine was usually done in one or two days and was successful in most of the cases. In the literature reported conversion ratio between fentanyl and buprenorphine is supposed to be even up to 1:2, fentanyl being twice as strong (μg/μg) as buprenorphine. In our clinical practice, however, we used a completely different conversion ratio 1: 0.5–0.66. After this conversion the pain intensity went up as in the first week witnessed by need of increased doses of other opioids. However, the dose of other opioids, without increasing the dose of buprenorphine patches settled in 1–2 weeks later. There were not enough patients in this cohort to say whether the conversion ratio was linear at all dose levels or not. It is possible that ratios 1:2 and 1:1 cited in the literature were derived immediately after conversion not taking into account long time-to-steady state characteristic for buprenorphine.

It is very difficult to say exactly which doses of additional opioids should be chosen to the dose of buprenorphine. Our survey did not give answer to this question. The doses of other opioids, either immediate or controlled release were in no way proportional to the dose of buprenorphine. So, patients on high doses of buprenorphine could still benefit from 5 or 10 mg morphine PRN. This was similar

for morphine and oxycodone. This is of particular interest as oxycodone is seen as not only μ-opioid receptor agonist, but also κ-opioid-receptor agonist [4, 13], while buprenorphine has partial μ-opioid receptor agonistic activity and κ-opioid receptor antagonistic activity [15]. If this κ agonistic activity was of importance, buprenorphine probably would show antagonism with oxycodone. This seems not to be the case.

Swapping from fentanyl to buprenorphine results in much lower doses of opioids needed to control pain. This suggests that fentanyl, at least in some cases may exercise a potent hyperlagesic effect which is missing in buprenorphine [16, 17]. In many cases after swap our patients revived and were not only pain free, but also showed much less neurotoxic effects (delirium, sleeplessness, confusion).

Conclusions

Transdermal buprenorphine offers certainly some new and attractive features. It is a difficult drug in the sense that pharmacological effects related to steady state are delayed for 1–2 weeks. Conversion ratio from fentanyl to buprenorphine should be certainly reviewed in the future. Approximately half of the patients treated with buprenorphine need other opioids, usually morphine or oxycodone. This is approximately the same as in the case of fentanyl. The dose of other opioids used with buprenorphine is highly variable and should be titrated starting from the very low doses. Buprenorphine is particularly interesting in case of inefficacy of fentanyl. However, problems with skin toxicity with buprenorphine patches are serious and some patients may develop skin toxicity and need discontinue therapy.

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