Buprenorphine in long-term control of chronic pain in cancer patients

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1. ABSTRACT

The aim of this randomized open-label prospective study was to evaluate the analgesic activity of buprenorphine in a transdermal formulation for cancer chronic pain control versus sustained-release morphine, in all cases combined with oral tramadol. A transdermal system with 35 µg/h buprenorphine was applied to the first group of patients (BT); the second group received 60 mg/day of sustained-release morphine (MT). In both groups oral tramadol was administered to a maximum of 200 mg daily, in case of need. The administration of transdermal buprenorphine versus morphine resulted in significant differences in the physical pain (P = 0.01), mental health (P = 0.03) and vitality (P = 0.001). These data indicated that the BT group showed an improvement of pain and a positive effect on the quality life.

2. INTRODUCTION

Cancer pain is a complex and multifactorial experience that implies a considerable disability for the patient. Therefore, it is a problem of enormous importance for health and social conditions (1). Drug therapy is based on the principle of the World Health Organization (WHO). WHO evidenced that switching from non-opioid analgesics to weak and strong opioids was safe and effective. Afterwards, an increasing number of guidelines regarding pain therapy, particularly opioids during the long-term treatment of moderate-severe pain, have been published by many national and international societies (2-3). These guidelines establish that drugs with different potency and mechanism of action could be used in a sequential way or in combination, in order to obtain a higher efficacy (4). Opioids are the most effective analgesics in the treatment of
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pain. However, the concern for a large number of side-effects, such as nausea, vertigo, constipation and respiratory depression, restrict their use. In case of overdose the activity of the respiratory center is progressively influenced, involving brain cortex before brain trunk. Before the opioid levels become enough high to inhibit the respiratory center, the patient develops a stuporous state and a scarce reactivity (5-6). Morphine is the most used pure opioid agonist. Its side-effects during prolonged chronic treatments are, however, a significant restraint to its usage (7). On the contrary, buprenorphine, a derivative of thebaine, is a partial agonist of μ-receptors, has an analgesic efficacy about 30-fold higher than morphine and shows a low incidence of respiratory depression, nausea and constipation (8).

Buprenorphine differs from the other partial agonists because can be administered by sublingual and transdermal routes (9). Application of transdermal devices with a polymeric active matrix, offers many advantages in terms of therapeutic efficacy and compliance. In fact, the continuous and controlled release of the main component by passive diffusion from the matrix enables to obtain a constant plasma concentration after the steady state, reducing the side-effects due to the plasma peaks resulting from repeated administrations. Transdermal buprenorphine has been used considering the characteristics of high lipophilia, low molecular weight and high affinity for specific pain receptors (10-12). Tramadol is a weak opioid obtained by synthesis, an agonist of μ-receptors, which also affects noradrenergic and serotoninergic neurotransmission. It may be administered by oral, parenteral or rectal route. Tramadol shows a lower incidence of cardiorespiratory depression and a reduced dependence compared to strong opioids. Therefore, it is particularly useful as analgesic of support of strong opioids limiting their doses and side-effects, but also as a valuable therapy for patients for whom the use of strong opioids is contraindicated (for example patients with respiratory insufficiency) (13-14). The aim of our study was to evaluate in patients with cancer chronic pain the analgesic effect of buprenorphine combined with tramadol by oral route versus sustained-release morphine always combined with oral tramadol.

3. MATERIALS AND METHODS

3.1. Population

The out-patient service where the study was carried out has received the approval by the steering committee. All the patients signed the informed consent before taking part in the study. Patients were selected for having cancer chronic pain for a period of 1 to 3 years, diagnosis of abdominal neoplasia and a pain score equal to at least 40 mm on the visual-analog scale (VAS) of Short-Form McGill Pain Questionnaire (SF-MPQ). Patients with a pain score average equal to at least 4 out of the 11 points on the Likert scale and with at least 4 observations recorded in the daily diary of pain during the previous week, were randomized. All the patients taking part in the study had previously received therapy with NSAID or other analgesic agents discontinuously without obtaining successful results. The exclusion criteria included:

- Presence of acute pain that could confound the evaluation and/or the self-evaluation of cancer pain;
- Intake of other experimental drugs within 30 days before the screening;
- Intake of antiepileptic agents (carbamazepine, phenytoin, sodium valproate, phenobarbital);
- Intake of Tricyclic antidepressants.

Moreover, we excluded patients with creatinine clearance ≤ 60 ml/min, in order to avoid dose adjustments (reductions), which would be necessary in patients with impaired renal function. Creatinine clearance was calculated on patients serum levels of creatinine using the following formula: adult male Crer = (140 – age in years) x weight in Kg / (72 x serum creatinine in mg/dl); and adult female Crer = [ (140 – age in years) x weight in Kg / (72 x serum creatinine in mg/dl)] x 0.85, where Crer was the creatinine clearance.

Furthermore, during the whole study the use of the following drugs was not permitted:

- Dextrometorphan
- Opioids
- Capsaicin
- NSAIDs
- Muscle relaxants
- Centrally acting OTC (over-the-counter) drugs

3.2. Design

This randomized open-label prospective study was divided into two phases: one week of screening and eight weeks of randomization and treatment.

3.3. Screening phase

At the first visit we established the eligibility of the patients and selected patients signed their informed consent. During the same visit, all the patients were required to fill the SF-MPQ. The family history was collected and physical and neurologic examinations were performed. Blood samples were taken to evaluate renal function (serum creatinine clearance). Selected patients received daily diaries to record pain and sleep and the relevant instructions to fill the diary.

3.4. Randomization and treatment phase

All the diaries kept during the screening phase were collected and reviewed. Patients once again completed the SF-MPQ at the end of the screening phase. The patients eligible for the study were randomized into blocks of 4, according to a computer-generated randomized code, to receive buprenorphine or morphine. Two groups, matching in age, general baseline conditions and staging degree of abdominal neoplasia, were formed. A transdermal system with 35 µg/h buprenorphine was applied to first group patients (BT) the first day and, in the event of an ineffective control of pain, the administration of tramadol by oral route was combined to a maximum of 200 mg. The patch was replaced every 72 hours. The second group received 60 mg/day of sustained-release morphine sulphate (MT) and tramadol was administered by oral route to a maximum of 200 mg daily, in case of need. In both groups, in
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case of VAS values > 40, the dose of strong opioid was increased (BT Group: 52.5µg/h of transdermal buprenorphine; MT Group: 90 mg of morphine sulphate daily).

All the patients were reminded by phone twice a week to fill in the daily diary as well as to report any side-effects.

3.5. Measures of efficacy and safety

Primary efficacy parameter was the evaluation of pain severity, recorded by the patients in the daily diaries using a 11-point Likert scale (0 = no pain; 10 = maximum possible pain). Secondary efficacy parameters were the points reached by SF-MPQ regarding the weekly average of interference with sleep, obtained by the daily sleep diary and Patient’s Global Impression of Change (PGIC). When patients waked up, they recorded in their diaries the information about pain and sleep related to the previous 24 hours.

SF-MPQ consisted of 3 sections: in the first section 15 items, which described pain occurring in the last week, were assessed from “0” (no pain) to “3” (acute pain), to quantify the past nociceptive experience (total score). The second section consisted of a 100 mm Visual Analog Scale (VAS), which evaluated patient’s pain during the last week, according to a scale ranging from “no pain” to “the maximum possible pain”. The third section was the Present Pain Intensity (PPI) Scale, which assessed pain by a 6-point scale ranging from “0” (no pain) to “5” (strongest pain). Interference with sleep was assessed by a 11-point scale, describing how pain affected patient’s sleep over the last 24 hours (0 = “no interference”; 10 = “impossibility to sleep due to pain”). PGIC was a test of global impressions of improvement based on a 7-point scale, by which patients considered any changes observed from the beginning of the treatment with an evaluation ranging from “much improved” to “much worsened”. Quality of life was instead established by Profile of Mood States (POMS) and by Short Form-36 Quality of Life (SF-36 QOL) Questionnaire. POMS consisted of 65 mood measurements taken the previous week, resulting in 6 mood assessments: tension/anxiety, depression/dejection, anger/aversion, strength/activity, fatigue/inertia and total mood disorder. SF-36 QOL Questionnaire measures each of the following 8 concepts of health: physical activity, limited activity due to physical problems, social activity, physical pain, general mental health, limited activity due to emotional problems, vitality and problems of general health. Safety of the protocol was assessed using data related to the side-effects (onset, intensity and relationship with the drug) and clinical parameters, such as heart rate, blood pressure and respiratory rate.

3.6. Statistical Analysis

The study potency was calculated by using G® Power software which gave an effect size of 0.80, a sample size of 52 patients and a study power equivalent to 0.80. Comparisons between the two groups studied were made by ANOVA and, if needed, corrections with Bonferroni’s test were performed to identify the significant differences. PGIC and side-effects were analyzed by the exact Fisher’s test. Data are shown as average and standard deviation (SD). The threshold for statistical significance was p< 0.05. Tests were performed with program SPSS, version 12.0 for Windows.

4. RESULTS

4.1. Population

After one week of screening 52 patients resulted eligible for our study. They were randomized and divided into two groups (26 patients everyone). Demographic, laboratory and patients pain characteristics are summarized in the Table (Table 1). The majority of patients in each group (BT; MT) reported a cancer chronic pain for at least 1 year. The average score of SF-MPQ VAS, SF-MPQ PPI, SF-MPQ total score, as well as the score related to the interference with sleep, were similar for both groups.

4.2. Efficacy measures

At each weekly visit, all the patients returned their diaries filled of data regarding the interference with sleep and the level of pain assessed by the SF-McGill Pain Questionnaire. In addition, at each visit an interview was done to fill PGIC, POMS and SF-36QOL Questionnaire.

We found significant differences between BT and MT groups at endpoint regarding the average score of pain, the average score of interference with sleep and the total scores of VAS, PPI and SF-MPQ (Table 2). When the results of each week were separately analyzed, there was a significant difference (p<0.01) in the average score of pain, from the 2nd to the 8th week, between the group treated with transdermal buprenorphine and that treated with morphine sulphate. Differences (p<0.01) were observed among randomized patients in the two groups also in the average score of the interference with sleep from the 1st to the 8th week (Figure 1 and Figure 2). According to SF-MPQ, patients who received transdermal buprenorphine showed an average score of total pain (total score) (p<0.01), VAS average score (p<0.01) and PPI average score (p<0.01) at the 2nd, 4th and 8th week, significantly lower compared to patients treated with morphine sulphate (Figure 3, Figure 4 and Figure 5). Considering the measurements on PGIC scale, patients who received transdermal buprenorphine obtained a significantly higher improvement than patients treated with morphine sulphate (Figure 6). About 65.4% of patients belonging to BT group achieved at least a “moderate” improvement at the end of the treatment on PGIC scale, while only 33% of patients of MT group showed the same level of improvement. Furthermore, one patient treated with buprenorphine reached a score of impairment according to PGIC scale, while the same score was reached by 7 patients who received morphine sulphate. Buprenorphine showed also a significant effect on 4 items of POMS (anger/aversion, p= 0.001; strength/activity, p= 0.001; fatigue/inertia, p<0.05; total mood disorder, p<0.05) versus morphine. Transdermal buprenorphine showed also a positive effect on the quality life, as it appeared from the significant differences versus morphine in the scores relative to physical pain (p= 0.01), mental health (p= 0.03) and vitality (p= 0.001) on SF-36 QOL Questionnaire. All the other items of the questionnaire on the quality life showed a positive effect of buprenorphine. No item was significantly different from those obtained with morphine sulphate.
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Figure 1. Evaluation of pain intensity (Likert scale 0-10)

Figure 2. Evaluation of pain interference with sleep (11-point scale)

Figure 3. Weekly evaluation of total nociceptive experience (15 items)

Figure 4. Weekly evaluation of painful symptomatology (100mm VAS)
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![Graph showing weekly evaluation of painful symptomatology (6-point scale).](image)

**Figure 5.** Weekly evaluation of painful symptomatology (6-point scale).

![Graph showing evaluation of reported patient’s perception of improvement (7-point scale).](image)

**Figure 6.** Evaluation of reported patient’s perception of improvement (7-point scale)

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical characteristics of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Age - years (mean±SD)</td>
</tr>
<tr>
<td>Duration of cancer chronic pain (years) (mean±SD)</td>
</tr>
<tr>
<td>Weight – kg (mean±SD)</td>
</tr>
<tr>
<td>Height - cm (mean±SD)</td>
</tr>
<tr>
<td>Creatinine clearance ml/min (mean ± DS)</td>
</tr>
<tr>
<td>Dull, profound pain</td>
</tr>
<tr>
<td>Burning, well localized pain</td>
</tr>
<tr>
<td>Tender pain, increased by movement</td>
</tr>
</tbody>
</table>

BT: transdermal buprenorphine group; MT: sustained-release morphine sulphate group
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Figure 7. Any changes in the analgesic therapy applied during the study.

Table 2. Baseline and end evaluation of painful symptomatology and patients’ quality life with cancer chronic pain treated with Buprenorphine TDS or morphine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group BT (26 patients)</th>
<th>Group MT (26 patients)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td>Baseline mean</td>
<td>Endpoint mean</td>
<td>Baseline mean</td>
</tr>
<tr>
<td>SF-MPQ VAS</td>
<td>6.4 ± 0.2</td>
<td>3.9 ± 0.3</td>
<td>6.5 ± 0.3</td>
</tr>
<tr>
<td>SF-MPQ total</td>
<td>20.5 ± 4.3</td>
<td>10.9 ± 3.2</td>
<td>21.0 ± 3.2</td>
</tr>
<tr>
<td>SF-MPQ PPI</td>
<td>2.4 ± 0.3</td>
<td>1.2 ± 0.2</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Interference with sleep</td>
<td>5.2 ± 0.2</td>
<td>2 ± 1.1</td>
<td>5 ± 0.3</td>
</tr>
<tr>
<td>SF-36 QOL - Physical pain</td>
<td>40.5 ± 5.2</td>
<td>55.2 ± 3.4</td>
<td>40.6 ± 4.6</td>
</tr>
<tr>
<td>SF-36 QOL - Mental health</td>
<td>72 ± 4.7</td>
<td>75.7 ± 3.1</td>
<td>72.5 ± 4.3</td>
</tr>
<tr>
<td>SF-36 QOL - Vitality</td>
<td>41.5 ± 5.6</td>
<td>53.5 ± 4.2</td>
<td>41.6 ± 5.7</td>
</tr>
<tr>
<td>POMS: Anger/aversion</td>
<td>9.6 ± 0.3</td>
<td>5.5 ± 1.2</td>
<td>9.5 ± 1.5</td>
</tr>
<tr>
<td>POMS: Force/activity</td>
<td>15.8 ± 1.5</td>
<td>17.5 ± 2.1</td>
<td>15.6 ± 1.6</td>
</tr>
<tr>
<td>POMS: Fatigue/inertia</td>
<td>12.8 ± 2.3</td>
<td>9.3 ± 2.1</td>
<td>12.4 ± 2.7</td>
</tr>
<tr>
<td>POMS: Mood total</td>
<td>39 ± 5.2</td>
<td>22.8 ± 4.6</td>
<td>39 ± 5.1</td>
</tr>
</tbody>
</table>

1The score increase means improvement; SF-MPQ VAS: Visual Analog Scale; SF-36 QOL: Short Form-36 Quality of Life; POMS: Profile of Mood States.

Table 3. Side-effects reported during the treatment with transdermal buprenorphine or morphine

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Group BT</th>
<th>Group MT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo</td>
<td>3</td>
<td>11</td>
<td>0.027</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>10</td>
<td>0.019</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>9</td>
<td>0.042</td>
</tr>
</tbody>
</table>

BT: transdermal buprenorphine group; MT: sustained-release morphine sulphate group; ns: no statistically significant

4.3. Additional doses of analgesic agents

Patients request for additional doses of analgesic agents was an important index of efficacy in our protocol. The final result observed pointed out that an increased analgesia from the first week of treatment was required by both groups. Patients requiring a higher analgesia with oral tramadol to a maximum of 200 mg/day were 42% (11 patients) vs 61% (16 patients) of BT and MT groups respectively, showing in this case a better analgesic coverage for both groups already from the first week of treatment. In particular, 7 patients of BT group required a dose equivalent to 100 mg of tramadol by oral route and 4 patients required 200 mg daily, to optimize the state of analgesia. Patients of MT group who required 200 mg/day of tramadol were 7 vs 9 patients who required 100 mg/day (Figure 7). During the second week the need of a higher
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analgesia, proved by a VAS value >40, was observed in about 11% (3 patients) of BT group vs 42% of MT group (11 patients). These patients received 52.5 µg/h of transdermal buprenorphine and 90 mg of morphine sulphate every day respectively (p< 0.05).

4.4. Protocol safety

At each weekly visit, protocol safety was assessed by monitoring key clinical parameters, such as heart rate, blood pressure and respiratory rate, which had no significant changes in both groups. The most frequent side-effects are showed in Table 3. The majority of the side-effects observed in patients who applied the transdermal system with buprenorphine were of mild or moderate entity.

5. DISCUSSION

Cancer patients, especially those with advanced and terminal stage disease, have pain as common symptom, characterized by a “total” pain, personal distress, with organic, psychological and social components in the pathogenesis. Therefore, a correct therapeutic approach cannot be exclusively the trivial and mechanical application of protocols and guidelines. 35-45% of patients suffer from pain at an early stage and/or already at the time of tumor diagnosis. About 70% of patients suffer from pain in an advanced stage of disease. Almost all the end-stage patients suffer from pain. The organic causes of cancer pain are different and may be directly related to the presence of tumor (for example compression and/or infiltration of nervous roots, visceral compression and/or infiltration, bone involvement, etc.) or indirectly (for example muscular contracture, lymph edema, paraneoplastic syndromes, etc.) and to the radiochemotherapeutic (for example mucositis) or surgical treatments (for example postoperative pain) (15). Also from a pathophysiologic point of view, cancer pain is very complex, identifying a nociceptive, somatic and visceral component, resulting from the activation of nociceptors at the level of somatic, superficial and deep, or visceral structures and a neuropathic component, resulting from a damage of Central Nervous System or Peripheral Nervous System (16). The therapeutic approach to this kind of chronic pain establishes the use of different drug classes, often in combination, to increase their efficacy and to reduce the doses and therefore the side-effects (17-18).

5.1. NSAIDs

These agents are a heterogeneous series of molecules that inhibit the synthesis of prostaglandins and the release of lysosomal enzymes. Their analgetic action is of peripheral type and is exerted exactly at the level of nociceptors. They are especially used for the control of pain caused by a mechanical compression of muscles, tendons, periostium (there is a huge release of prostaglandins in these forms of pain), but they have a lower effect on visceral pain. The major side-effects are gastrointestinal diseases, coagulation disorders and functional renal impairment (19-20).

5.2. Opioids

These agents are often indispensable in the therapy of cancer pain. Their powerful analgesic activity is due to the interaction with receptors present in CNS areas and in spinal cord along the sensory pathways of pain. The different activity of a single molecule (intensity and duration of action, side-effect) may be explained considering the existence of many varieties of receptors and the different ability of each molecule to interact with a single receptor.

µ1-receptors are in the supraspinal area and exert mainly an analgesic activity; µ2-receptors are above all responsible for the side-effects ascribed to opioids (respiratory depression, gastroenteric and cardiocirculatory effects), κ-receptors are in the spinal cord and brain cortex and are responsible for analgesic and side-effects of sedation and miosis; δ-receptors are in the spinal cord exerting an analgesic activity.

Morphine may be administered by parenteral route (i.m./s.c.) or by oral route (10 mg of i.m./s.c morphine. are equivalent to 20-60 mg by oral route). It exerts a prevalent action at the spinal cord level, whereas buprenorphine at the supraspinal level. This was the rationale of many recent studies in which the two drugs were used in combination, despite the recommendations made by the majority of guidelines (21-23). This could allow to a morphine dose reduction with a lower incidence of side-effects. In Italy there is a strong bias against the use of morphine for long-term treatments, due to the concern for addiction and tolerance. Actually tolerance, defined as the need of an increasing drug amount to obtain an equivalent analgesic effect, occurs not only to analgesia, but also to side-effects. Addiction, defined as a change of physiological conditions characterized by symptoms of withdrawal, which occurs when therapy is abruptly discontinued, is reduced by some opioids, such as buprenorphine. Buprenorphine, which is increasingly employed, is a partial opioid agonist with a high affinity for µ and κ-receptors and has potency 25 to 50-fold higher than morphine. Buprenorphine taken at therapeutic doses does not show the so-called “ceiling effect” (it seems that this effect appears at doses > 4 mg/day), further dose increase enhances the side-effects, which are partially reversible with naloxone administration (24-25). In Italy buprenorphine is currently administered by sublingual route at the dose of 0.2 to 0.4 mg every 6 to 8 hours with an analgesic action appearing within 15 to 45 min, or in vials of 0.3 mg for intravenous use. Recently, a transdermal system with 35, 52.5 and 70 µg/h of buprenorphine, equivalent to 0.8 mg, 1.2 mg and 1.6 mg respectively for 24 hours, has become available (35 µg/h of transdermal buprenorphine is equivalent, in terms of equianalgesic potency, to 10 mg of i.m./s.c. morphine and therefore to 20-60 mg of morphine by oral route). This route of administration met the favor of both patients and physicians, because permits a steady plasma concentration with an unchanged therapeutic efficacy over hours and reduces side-effects caused by plasma peaks (“bolus effect”) due to repeated administrations. Another opioid, largely used in the control of neoplastic pain, is tramadol. Apart from acting on opioid receptors, tramadol has effects on noradrenergic and serotoninergic neurotransmission at
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the level of the descending system inhibiting nociceptive messages transmission (similar to tricyclic antidepressants), and also has a lower incidence of respiratory depression and other side-effects compared to strong opioids.

5.3. Adjuvant drugs

The adjuvants are a heterogeneous group of non-analgesic drugs, different in their structure and mechanism of action. They are largely used to control cancer pain, especially the psycho-affective and behavioral component. The most widely used are Benzodiazepines, particularly for their anxiolytic effect, Amitriptyline, a tricyclic antidepressant, used to obtain an elevation of the mood tone, Carbamazepine, an anticonvulsant, especially used in the treatment related to nerve damage (nerves neoplastic invasion, neuropathy, post-amputation painful syndrome) (26). Apart from following the WHO, the choice of the drug should consider cause, quality, intensity of pain, presence of metastases and progression of disease. For an effective therapeutic schedule is important to recognize the mechanisms cause of pain, distinguishing nociceptive, neuropathic and mixed components, in order to make the right choice. In our study we assessed the analgesic activity of transdermal buprenorphine combined with oral tramadol for long-term control of cancer chronic pain, versus the administration of sustained-release morphine, always combined with oral tramadol. The data proved that buprenorphine was more effective than morphine and above all was better tolerated by the patients. The onset of side-effects was lower in BT group than in MT group (42% vs 62%) and when they occurred there was also a difference in their intensity and in patient’s tolerability.

Intensity of adverse reactions was, in fact, lower in patients of BT group than in patients of MT group, requiring in the latter more frequent use of symptomatic drugs (metoclopramide for vomiting or laxatives for constipation). In particular, especially for side-effects at the gastrointestinal level, a key role was played by the route of administration. Morphine, taken by oral route, showed a remarkable incidence of episodes of constipation caused by the action on intestinal receptors. This event did not occur with the administration of buprenorphine by transdermal route. Considering the “convenience” of the route of administration (transdermal for buprenorphine and oral for morphine), transdermal route appeared to be better tolerated by patients. Moreover, we found an improvement in the quality and in the amount of sleep in BT group versus MT group, which could appear as a side-effect (excessive sedation), but is actually the evidence of the recovery of a physiological activity invalidated for a long time, considering also the remarkably worsened state of general and psychological conditions of cancer patients (27-28). For all the above reasons, we thought it is not appropriate that many physicians are still currently suspicious of the use of opioids in a long-term treatment of cancer chronic pain. If opioids are properly used, they remarkably improve patients’ quality life. A key principle still remains the "different response" to therapy related to the patient’s conditions (individual susceptibility, hepatic and renal function). Therefore, we suggest to "modulate" the therapy according to the individual needs.

6. REFERENCES


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**Key Words:** Transdermal Buprenorphine, Chronic Cancer Pain, Sustained-Release Morphine Sulphate, SF-MPQ

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