ACTA MEDICA SALINIANA

ORIGINAL PAPER

Cancer Pain: Comparison of Oral Morphine and Transdermal Fentanyl Treatment

[1]Samir Husic, [2]Dzenita Ljuca

ISSN 0350-364X

Husic et Ljuca. Acta Med Sal 2011; 40(1); 7-12.
DOI: 10.5457/ams.176.10

Aim. The aim of the research is to compare the efficiency of equianalgesic dosages of transdermal fentanyl and oral morphine in severe cancer pain treatment in patients with or without bone metastasis.

Patients and methods. 80 patients who were treated with transdermal fentanyl and oral morphine due to severe cancer pain (from 7 to 10 on the NRS scale) were examined in a prospective research conducted at the Palliative care centre (hospice) of University Clinical Centre Tuzla. We compared the efficacy of equianalgesic doses of transdermal fentanyl and oral morphine in pain treatment.

Results. The Karnofsky score for all 80 patients upon admission was 47.13 ± 11.05 and 51.25 ± 11.73 upon discharge ($p = 0.0005$). In patients with and whitout bone metastases neurophatic and nocioceptive pain were dominant ($p < 0.05$). Mean pain intensity in all patients on the first day of treatment was 9.00 (from 7.00 to 10.00) which is higher compared with pain intensity on the tenth day (0.9 ± 0.98) of treatment ($p < 0.0001$). On the second day of the treatment mean pain intensity was lower in patients from the control group, (median 4.00; from 2.00 – 6,00) compared to patients from the test group (median 5.00; from 3.00 – 7.00).

Conclusion. With constant pain evaluation, treatment should be started with fast releasing oral morphine. After the stabilization of basic pain with oral morphine, better effects, with less side-effect are obtained with equianalgesic doses of transdermal fentanyl.

Keywords. *cancer pain, morphine, transdermal fentanyl*

INTRODUCTION

Pain is undoubtedly an unpleasant feeling and motivation wise it has a character of punishment. International Association for the Study of Pain – IASP, founded in 1973, published an official pain definition which states the following: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage"[1]. The definition speaks of dual meaning of the term pain, of existence of sensory qualities but also of distinctively individual and complex experience whose intensity is influenced by previous learning, the state of nervous system in the moment of experiencing it, and so on.

Acute pain has a known etiology, it is transient, followed by a metabolic response of the whole organism and is easily treatable by removing the etiological factor. Chronic pain which lasts up to 6 or more months is a sign of a chronic disease. It influences the patient's behavior, sleep, social function and it is an illness in itself with its symptoms, syndromes and complications.

Around 30 – 40 % of cancer afflicted patients experiences pain already at establishing the diagnosis, while in advanced stage of the disease 75% - 90% of patients endures pain which speaks for the underestimation of cancer pain, despite the information from the institutions of palliative medicine from all over the world, which state that in 95% of the cases cancer pain can be efficiently controlled [2,3]. In 70% of the cases pain is caused by the carcinoma itself. Compression and nerve damage by carcinoma and pain due to bone metastasis with the infiltration of the bone nerve are the cause of neuropathic cancer pain[4]. Disorder of balance between activity of osteoclasts and osteoblasts, change of normal bone turnover leads to osteolysis, micro fractures or pathological fractures[5]. In about 20% of the cases, the pain is caused by cancer treatment[6]. Surgical interventions can cause nerve damage, chemotherapy, releases cytokines which sensibilizes nociceptors, radiotherapy leads to tissue fibrosis with nerve compression and painful mucositis can be caused both by chemotherapy and radiotherapy. Stimulation of nociceptors caused by cancer and prolonged triggering in the neurons with C-receptors causes activation of N-methyl D-aspartate (NMDA) receptors resulting in central sensitization, which, along with peripheral sensibilization can lead to occurrence of allodynia[7]. Bone metastasis are one of the most frequent painful syndromes

Institutions
[1]Center for Palliative Care (Hospice)
[2]Gynaecology and obstetrics clinic

University Clinical Center Tuzla
Tuzla, Bosnia and Herzegovina

Received
05.10.2010
Accepted
17.03.2011

Corresponding author
Samir Husić
University Clinical Center Tuzla
Center for Palliative Care
Trnovac bb, 75000 Tuzla
Bosnia and Herzegovina

drsamirhusic@gmail.com

Competing interests
The authors declare no competing interests.

Table 1. General and demographic characteristics of the examinees

Groups		Test group (TD* fentanyl)	Control group (oral morphine)	In total
Number of patients		40	40	80
Age		59.61 ± 9.43	60.22 ± 11.02	59.91 ± 10.19
Sex	M (%)	27 (33.75)	23 (28.75)	50 (62.5)
	F (%)	13 (16.25)	17 (21.25)	30 (37.5)

**TD - transdermal*

in patients in advanced stages of carcinoma disease. In 70% of the cases this pain is difficult to control, while about 50% of the patients die without adequate pain management and poor life quality. Bone metastasis are often combined with so called skeletal related events –SRE-s which include severe pain fractures, the need for surgery or radiotherapy, compression of the spinal cord or demineralization of the bone[8].

Morphine is an opiate of choice for patients with medium to severe cancer pain[9]. It is well absorbed after oral application with metabolization in the liver in M3G (morphine 3-glucuronide) without and M6G (morphine 6-glucuronide) with strong analgesic and sedational effect[10]. Fentanyl is a synthetic opoioid, with effects typical for all narcotics: analgesia, respiratory depression, cough inhibition, miosis and sweating[11]. Fentanyl is 80 to 100 times stronger than morphine so that a dose of 25 μg/h of fentanyl corresponds to 25 to 60 mg/day oral morphine, a dose of 50 μg/h of fentanyl corresponds to 61-115 mg/day oral morphine etc. Fentanyl in a form of transdermal preparations (TTS - transdermal therapeutic system) in the USA has been in use since 1992 and since 1995 in Germany [12]. The aim of the research is to compare the efficiency of equianalgesic dosages of transdermal fentanyl and oral morphine in severe cancer pain treatment in patients with or without bone metastasis.

PATIENTS AND METHODS

A prospective study involved 80 patients, hospitalized in the Hospice for recumbent patients at Palliative care centre of public health institution of University clinical centre in Tuzla, in the terminal stage of the cancerous disease, who were treated with strong opioids due to their unbearable cancer pain (from 7-10 according to NRS scale) without previously using these medications in their therapy (morphine, fentanyl). 33.8% (27 patients) of which were patients with lung tumor, 27.5% (22 patients) with digestive tract tumor, 12.5% with breast tumor, 11.3% with ORL tumor, while tumors of other organs were represented with less than 10%. Fourty examinees (20 from test and 20 from control group) had verified bone metastases. The average age was 59.91 ±10.19, 50 (62.5%) of the patients were male and 30 (37.5%) were female (Table 1).

Breakthrough pain in both groups of examinees is treated by additional dosages of oral morphine (8 mg in form of morphine hydrochloride solution). Test group consisted out of 40 patients who were set under therapy of transdermal fentanyl of 25 μg after their pain intensity was established above 7 according to NRS. On the fourth and seventh day pain evaluation was conducted, so the dosage of transdermal fentanyl was increased to 50 μg (on the fourth day) or 100 μg (on the seventh day) if there had been 2 or more breakthroughs of pain the previous day that required the "salvage dose". Control group consisting of forty patients whose pain was undurable (above 7 according to NRS scale) was treated with 48 mg of oral morphine (divided into 6 dosages - 8 mg every 4 hours). On fourth and seventh day there has been pain evaluation recorded, as well as the regular dose of morphuim, increased by 50 per cent if there has been more than two breaktroughs of pain which demanded „salvage dose". Patients excluded from the study were those with cancer pain intensity 6 or lower than 6 according to NRS scale; those with allergies to strong opioids; if they have used strong opiates before diagnosis of tumorous disease or during the treatment of cancer pain before the admission to Hospice; patients who experienced regurgitation which prevents the possibility of taking oral morphine;

Table 2. Pain character according to LANS scale in both groups of patients

Patient group	Bone metastasis	Type of pain (%)		
		Nocioceptive	Mixed	Neuropathic
Test group	yes	7 (8.8)	2 (2.5)	11 (13.8)
	no	12 (15.0)	6 (7.55)	2 (2.5)
Control group	yes	8 (10.0)	7 (8.8)	5 (6.3)
	no	12 (15.0)	5 (6.3)	3 (3.8)
In total	yes	15 (18.8)^{A}	9 (11.3)^{B}	16 (20.0)^{C}
	no	24 (30.0)^{D}	11(13.8)^{E}	5 (6.3)^{F}
∑		39(48.8)^{G}	20 (25.0)^{H}	21 (26.2)^{I}

$p = 0.27$ comparing ^{A}with^{B};$p = 0.02$ comparing ^{D}with^{E};$p = 0.0002$ comparing ^{D}with^{F};
$p = 0.14$ comparing ^{A}with^{D};$p = 0.02$ comparing ^{C}with^{F};$p = 0.003$ comparing^{G}with^{H};$p = 0.005$ comparing ^{G}with^{I}

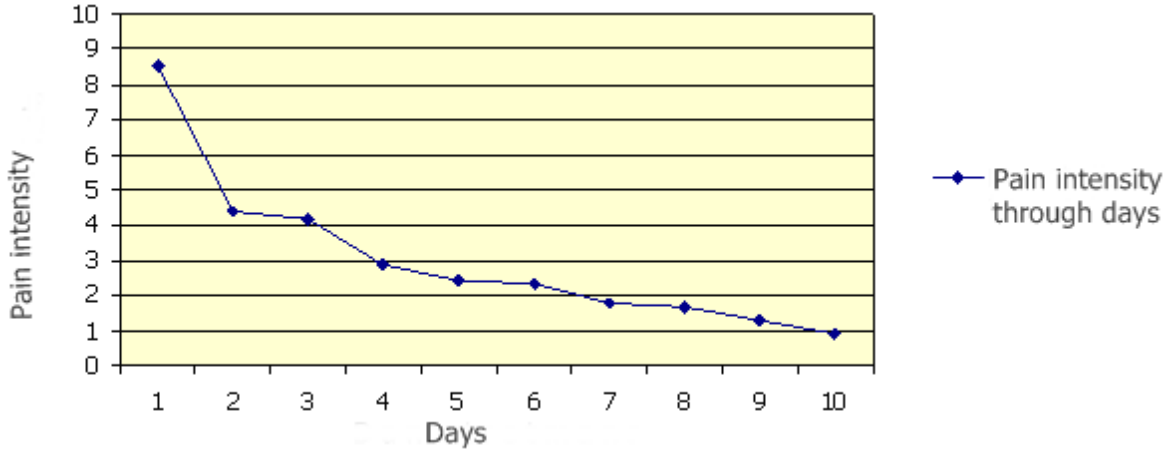

Figure 1. Mean pain intensity through days in all tested patients

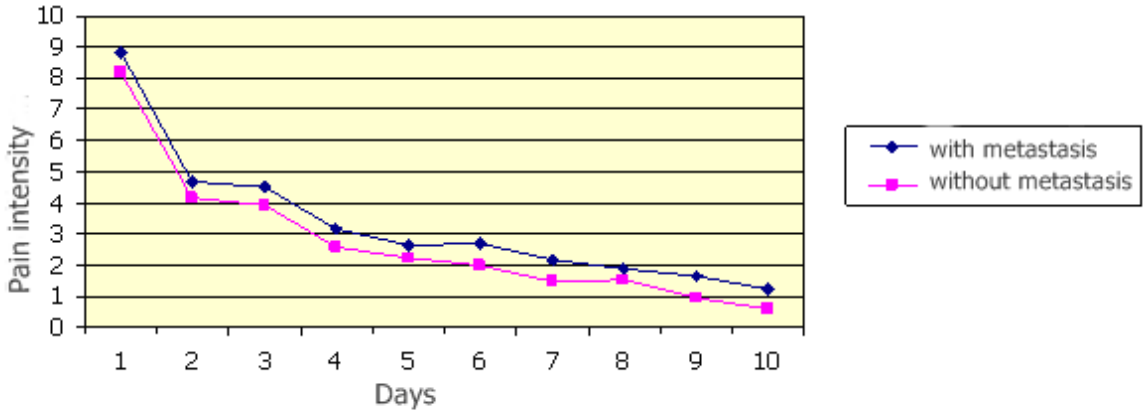

Figure 2. Pain intensity through days of patients with and without bone metastasis

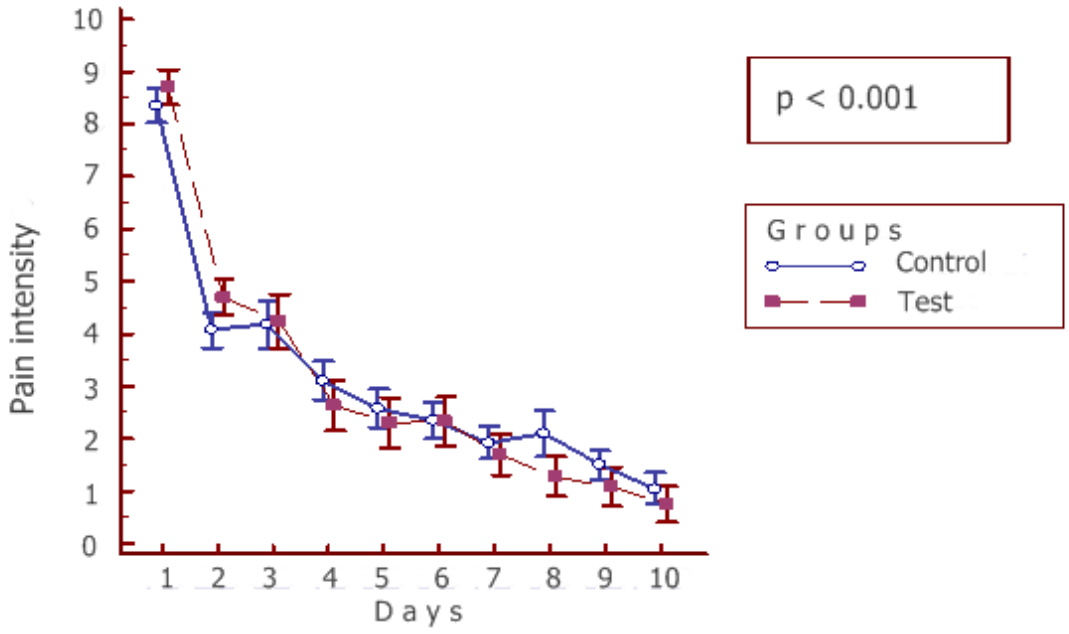

Figure 3. Pain intensity through days for the patients from test and control group

with pronounced signs of respiratory, renal or liver insufficiency. Upon the admission of the patients to the Palliative care centre (hospice), for all 80 patients the following was established: general state of the patients (Karnofsky score), pain intensity (NRS scale: 0 points – no pain and 11 points – worst possible pain) and pain character (LANSS scale- to 8 points - nocioceptive characteristic of the pain; 9 – 12 points - mixed pain and higher then 12 points – neuropathic pain).

STATISTICAL ANALYSIS

Statistical analysis was conducted using biomedical application software called MedCalc for Windows version 9.4.2.0. For testing the repeated measurement of paired samples, depending on the distribution of variables, paired T-test and Wilcoxon tests were used. For testing the repeated measurements of samples with more than 2 variables, ANOVA for repeated measurements was used. For testing the hypothesis of difference in frequency of parameters of dichotomous scale, the test used was $\chi 2$ test. Statistical hypothesis were tested based on the level of significance of $\alpha = 0.05$ meaning that the difference between samples was considered to be significant if $p < 0.05$.

RESULTS

There was neither statistically significantly difference in age ($p > 0.05$) nor in sex ($p > 0.05$) between the test and the control group of patients. Mean value for Karnofsky score for all 80 patients upon admission was 47.13 ± 11.05 and on discharge 51.25 ± 11.73, and after relieving the pain Karnofsky score was statistically significantly better ($p = 0.0005$). In patients from test group mean value of Karnofsky score on admission was 46.75 ± 11.63, while on the tenth day of treatment it was statistically significantly better ($p = 0.0006$) on average 52.25 ± 12.29. In patients from control group on the tenth day of treatment mean value for Karnofsky score was 46.67 ± 11.21 so there was no statistically significant difference ($p = 0.059$) compared to the first day when the mean value for Karnofsky score was 47. 5 ±10.56. There was no statistically significant difference when comparing mean values of Karnofsky score of the patients from the control group and patients from the test group on the day of the admission ($p = 0.67$), as there was no statistically significant difference ($p = 0.45$) on the discharge. Out of all patients in 39 of them (48.8%) the sum of points according to LANSS scale was lower than 8 which indicates to nocioceptive characteristic of the pain, which is statistically significantly more compared to 20 patients (25.0%) with mixed pain ($p = 0.003$, $\chi 2 = 8.74$) and 21 (26.2%) with dominant neuropathic painful component ($p = 0.005$ $\chi 2 = 7.78$) (Table 2).

In the group with bone metastasis 15 patients (18.8%) were with dominant nociceptive component and there was no statistically significant difference compared to the number of patients with neuropathic (16 patients or 20%) or mixed nociceptive - neuropathic pain (9 patients or 11.3%). Patients who had not had verified bone metastasis had dominant nociceptive pain (24 patients or 30%) which was statistically significantly more compared to 11 patients (13.8%) with mixed ($\chi 2=5.23$) and 5 patients (6.3%) with neuropathic pain ($\chi 2=13.57$). There was no statistically significant difference in the percentage of patients with and without bone metastasis in whom the nociceptive pain was dominant ($\chi 2=2.147$) but there was statistically significantly greater number of patients who had bone metastasis compared to those patients who did not, with dominant neuropathic component of pain ($\chi 2=5.43$) (Table 2).

Mean pain intensity in all 80 examined patients on the first day of treatment was 9.00 (from 7.00 to 10.00) which was statistically significantly higher compared to the pain intensity on the tenth day of treatment which was 0.9 ± 0.98. Test of within-subjects effects showed significant downword trend ($p< 0.001$). Already after 24 hours of cancer pain treatment with strong opioids pain intensity was significantly lower ($p<0.0001$) . The only measurements not showing statistical differences were between 2 – 3 day, 5 – 6 day, 7 – 8 day and 8 – 9 day (Figure 1).

Pain intensity was higher in the group with bone metastases as compared with the group without them, during the entire study period (Figure 2). Test of between-subjects effects showed significant difference ($p = 0.001$). Likewise, test of within-subjects effects was also significant when testing for factor ($p < 0.001$). However, when testing for the group and factor interaction, there was no difference ($p > 0.05$), which means that the rate of falling trend of pain intensity was the same in both groups.

Test of between-subjects effects showed no difference in pain intensity between the test and control group ($p > 0.05$). However, when testing for the group and factor interaction, the difference was significant, which means that the rate of falling trend in pain intensity was higher in the test group ($p < 0.001$)(Figure 3). On the day of the admission there was no statistically significant difference ($p = 0.14$) in the pain intensity between the patients of test (median = 9.00; from 7.00 to 10.00) and control group (median = 8.00; from 7.00 to 10.00). However, on the second day of the treatment mean pain intensity, outside the breakthrough pain was significantly lower ($p = 0.01$) in patients from the control group, who were treated with oral morphine (median 4.00; from 2.00 – 6.00) compared to patients from the test group, treated with transdermal fentanyl (median 5.00; from 3.00 – 7.00).

In the following days (from 3rd to 7th day) there was no statistically significant difference in pain intensity in test and control group. On the eighth and ninth day mean of total pain intensity was statistically significantly lower in patients treated with transdermal fentanyl compared to patients who received oral morphine [on the eighth day $p = 0.005$ in comparison to 1.27 ± 1.19 in patients from test and 2.10 ± 1.37 in patients from the control group; on the ninth day $p = 0.04$ in comparison to 1.00 (1.00 - 2.00) patients from test and 1.50 (1.00 - 2.00) patients from the control group](Figure 3).

Upon the completion of the study on the tenth day of

the treatment there was no significant difference (p = 0.08) in pain intensity between the patients of test and control group.

DISCUSSION

In our study the mean value for Karnofsky score for all 80 patients after relieving the pain Karnofsky score was statistically significantly better. Moreover, when comparing Karnofsky score it was significantly better on the day of admission compared to the day of the discharge in patients from the test group, while there was no statistically significant difference in patients from the control group. In a study which monitored the effects of cancer pain treatment by transdermal fentanyl within 3 months, Karnofsky score was relatively constant during the treatment, with mean value of 68 ± 2 at the end of the second month and 69 ± 2 at the end of the study[13].

In our study 48.8 % of the patients had dominant nociceptive pain, statistically significantly higher compared to patients with mixed pain, and compared to patients with dominant neuropathic painful component. Statistically significantly larger number of patients with bone metastasis compared to patients without them, has neuropathic pain. Similar results are shown by a study conducted on 77 patients with cancer diseases (where GI tumors are dominant with 65.1%) with predominance of nociceptive (visceral) pain in 68 (88.3 %) patients, mixed (nociceptive somatic + neuropathic pain) in 8 (10.4%) patients and exclusively just neuropathic pain in 1 patient (1.3%)[12].

A research conducted in Greece on all "opioid –naive" patients with cancer pain treated with transdermal fentanyl, shows a mean value of pain intensity upon admission 7.1 ± 1.7[14]. Patients were treated by transdermal fentanyl of average dose of 36.5 ± 15.7 μg/hour (patches of 25 and 50 μg). On the third day of the treatment 84% (95) of the patients had a pain intensity of ≤ 3 (mean value 0.5 ± 0.8), 12.4% (14 patients) rated the pain with grade 4, and 4 of the patients (3.5%) rated the pain intensity with grades 5 - 8. On the seventh day and until the completion of the study (which lasted for 42 days) pain intensity had mean values of 1.3 to 0.16, while the average dose of fentanyl was 122.1 ± 81.2 μg/h. In our study in patients whose basal cancer pain was treated with transdermal fentanyl, pain intensity on the fourth day of treatment was statistically significantly lower than in controls and it showed the value of 2.6 ± 1.53. Comparing the pain intensity of control group and test group of patients it is notable that the pain intensity is higher within the first three days in patients treated by a transdermal fentanyl and on the fourth day until the end of the study mean pain intensity was higher in patients treated with oral morphine. Similar results are shown by a study conducted on 33 patientswhose cancer pain was treated with transdermal fentanyl as only strong opioid[15]. On admission mean pain intensity was 8.33 ± 1.02, and on the fourth day of treatment with transdermal fentanyl (TDF) it was significantly reduced to 2.06 ± 1.34 (p < 0.0001), and on the tenth day to an average of 0.55 ± 0.75.

In a study Cerezo et al., conducted on 40 patients, the mean pain value on the first day was 7.14 and within 72 hours it was reduced to 2.40 and on the seventh day of treatment by TDF it was reduced to 2.07 (p = 0.002), with high percentage of patients satisfaction (89%) primarily related to simplicity of the usage[16]. A study conducted in China on 485 patients with strong cancer pain, the starting pain value was 7.92. After introducing TDF, on the first day already 86.3% of the patients reported pain relief (the mean intensity 3.58; p < 0.001). On the sixth day of treatment the mean pain intensity was reduced to 3.06 and on the ninth day to 1.29. In the same study in patients with bone metastasis the starting pain intensity was 8.25 and it had not significantly differed compared to patients without meta changes in their bones and it was (7.92)[17]. In our research the starting pain intensity in patients with meta changes in their skeleton was statistically significant difference compared to patients without meta changes in their bones. In patients with bone metastasis compared to those patients without the metastasis pain intensity was higher for all the following days until the end of the study (on the tenth day).

The mean pain intensity established by a numerical scale, in the control group (treated with oral morphine) on the first day was 8.00, whereas it was significantly lower on the second day with constant reduction of intensity until the tenth day. Similar results are shown in several studies. In one of those studies conducted on 172 patients in Italy starting pain intensity was 7.4 ± 1.3, and on the fifth day of treatment with oral morphine it was reduced to 3.8 ± 1.5 (p < 0.0001)[18]. In another study from 2008 conducted on 159 patients with severe cancer pain, it is claimed that in the titration phase of oral morphine treatment (5 mg per 4 hours) within three days pain management is obtained in 50 % and within 5 days in 75% of the patients[19]. Pain intensity reduces from 7.36 points in the beginning (according to NRS numerical scale) to 2.43 on the third, and 1.67 points on the fifth day (p < 0.001). In a study conducted on 35 hospice patients with severe cancer pain treated with oral morphine the mean pain intensity on the first day of hospitalization was 8.23 ± 1.06 and on the second day of treatment it was significantly lower compared to the day of the admission (p < 0.0001), and on the tenth day mean value was 1.23 ± 1.06[20].

In conclusion, nocioceptive pain was dominant in patients with advanced cancer. However, bone metastasis often causes the appearance of neuropathic pain. With constant pain evaluation, treatment should be started with fast releasing oral morphine, which enables a safe titration and effective pain relief of basic pain. After the stabilization of basic pain with oral morphine better effects are obtained with equianalgesic doses of transdermal fentanyl, with relieving of breakthrough pain with "salvage doses" of fast releasing strong opioid.

LIMITATIONS OF THE RESEARCH

In a study design, the time frame of monitoring the test subjects should be prolonged and continue until

the completion of hospitalization. The sampling was not based on randomization. The effects of transdermal fentanyl and short-lasting morphine should be compared to those of long lasting and slow releasing opioids. Intensity and frequency of side effects can be related to a choice of analgesic therapy, so those effects, along with cardiovascular and respiratory system should be monitored.

REFERENCES

1. "IASP Pain Terminology". International Association for the Study of Pain. http://www.iasppain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728#Pain.Retrieved 2 September 2009.

2. Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. Ann Oncol.2005;16(supp 4):132-5. doi:10.1093/annonc/mdi922; PMid:15923413

3. Weiss SC, Emanuel LL, Fairclough DL., et al., Understanding the experience of pain in terminally ill patients.Lancet.2001;357(9265):1311-5. doi:10.1016/S0140-6736(00)04515-3

4. Delaney A, Fleetwood-Walker SM, Colvin LA, Fallon M. Translational medicine: cancer pain mechanisms and management. Br J Anaesth.2008;101(1):87-94. doi:10.1093/bja/aen100; PMid:18492671

5. Colvin L, Fallon M.Chalenges in cancer pain management: bone pain. Eur J cancer.2008; 44(8):1083- 90. doi:10.1016/j.ejca.2008.03.001; PMid:18439817

6. Manttyh PW, Nelson CD, Sevcik MA, Luger NM, Sabino MA. Molecular mechanisms that generate and maintain cancer pain. In: Dostrovsky J.O., Carr D.B., Koltzenburg M., editors. Proceedings of the 10 th World Congress on Pain. Seatle: IASP Press,2003.663-81.

7. Clivatti J, Sakata RK, Machado A. Review of the use of Gabapentin in the Control of Postoperative Pain; Revista Brasileira de Anestesiologia.2009;59(1):87 - 98. PMid:19374220

8. Coleman R. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27(3):165-76. doi:10.1053/ctrv.2000.0210; PMid:11417967

9. Zorc B. Opioidni analgetici. Kem. Ind.2004;53(5):209–216.

10. Gretton S, Riley J. Morphine metabolites: a review of their clinical effects. European Journal of Palliative Care.2008;15(3):110 -14.

11. Agarwal S, Polydefkis M, Block B, Jennifer Haythornthwaite J, Raja SN. Transdermal Fentanyl Reduces Pain and Improves Functional Activity in Neuropathic Pain States. Pain Medicine.2007;8(7):554 - 62. doi:10.1111/j.1526-4637.2006.00246.x; PMid:17883740

12. Clemens KE and Klaschik E. Clinical Experience with Transdermal and Orally Administered Opioids in Palliative Care Patients - A Retrospective Stud. Japanese Journal of Clinical Oncology.2007;37(4):302 – 9. doi:10.1093/jjco/hym017; PMid:17519302

13. Sloan P, Moulin DE and Hays. A Clinical Evaluation of Transdermal Therapeutic System Fentanyl for the Treatment of Cancer Pain. Journal of Pain and Symptom Management. 1998;16(2):103 - 111. doi:10.1016/S0885-3924(98)00044-X

14. Mystakidou K, Befon S, Tsilika E, Dardoufas K, Georgaki S, Vlahos L. Use of TTS fentanyl as a single opioid for cancer pain relief: a safety and efficacy clinical trial in patients naive to mild or strong opioids.Oncology.2002;62(1):9-16.doi:10.1159/000048241; PMid:11810038

15. Ljuca Dz i Husic S, Treatment of severe cancer pain by transdermal fentanyl. Bosnian Journal of Basic Medical Sciences.2010;10(2):158 - 64. PMid:20507298

16. Cerezo L, Marin A, Zapatero A, Martín de Vidales C, López M, Pérez-Torrubia A. Prospective clinical evaluation of transdermal fentanyl for the treatment of cancer pain. Journal Clinical and translational oncology.2000;2(3):159-63.

17. Yu Shiying. Transdermal fentanyl for the treatment of cancer pain: A multicenter study. The Chinese- German Journal of clinical oncology.2003;2(2):114-7.doi:10.1007/BF02855661

18. Gatti A, Reale C, Occhioni R, Luzi M, Canneti A, De Polo C, Gubernari M, Mammucari M, Fabrizio Sabato A. Standard therapy with opioids in chronic pain management : ORTIBER study. Clin Drug Investig.2009;29(Suppl 1):17-23. doi:10.2165/0044011-20092900l-00003; PMid:19445551

19. De Conno F, Ripamonti C, Fagnoni E, Brunelli C, Luzzani M, Maltoni M, Arcuri E, Bertetto O. The MERITO Study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain. Palliative Medicine.2008;22(3):214-21. doi:10.1177/0269216308088692; PMid:18477715

20. Ljuca Dz i Husic S. The effects of oral morphine in „titration phase" of carcinoma pain treatment. HealthMed.2010;4(2):434 - 40.

Citation friendly format:
Samir Husic, Dzenita Ljuca. Cancer Pain: Comparison of Oral Morphine and Transdermal Fentanyl Treatment. Acta Medica Saliniana 2011;40:7-12. DOI:10.5457/ams.176.10