



TREATMENT OF SEVERE CANCER PAIN BY TRANSDERMAL FENTANYL

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ABSTRACT

The goal of research was to determine the frequency, intensity, time of occurrence, duration and causes of breakthrough pain (BTP) in patients whose carcinoma pain was treated by transdermal fentanyl. (TDF). A prospective study was conducted in a hospice for recumbent patients of the Centre for Palliative Care (hospice) University Clinical Centre Tuzla from October 2009 to December 2010. 33 patients in terminal stage of carcinoma, who had been treated by transdermal fentanyl due to their excruciating pain (7-10 mark on numerical scale) with initial dosage of 25 µg as a strong opiate analgesic, were monitored within the time period of 10 days. In the statistics we used the even T - test, the Wilcoxon test and Mann-Whitney test. The difference was seen to be significant at $p < 0,05$. Treatment by transdermal fentanyl significantly reduces the intensity of strong carcinoma pain ($p < 0.0001$), with a frequent requirement for dose increase with bone metastasis. The intensity of BTP is higher compared to the pain experienced upon reception. The frequency and intensity of BTP are significantly reduced already in the second day of treatment by transdermal fentanyl ($p = 0,0024$). The BTP is most intense in patients with neck and head tumours ($9,26 \pm 0,66$), and most frequent with abdomen and pelvic tumour. The biggest number of BTP (68.3 %) occurs within first three days of treatment. BTP most frequently occurs in the evening or at night (between 18:00 and 06:00 h in 62,2 % of the cases), with the duration of usually less than 15 minutes (65,2% of the cases). In 61,6 % cases the occurrence of BTP is related to physical activities or psychosocial incidents, while the cause is undetermined in 38,4 % of examinees.

BTP is most frequent within first three days of treatment by TDF. Using the optimal dosage a good control of carcinoma pain is enabled, regardless of the occurrence of bone metastasis, while it also helps reduce the frequency and intensity of BTP.

KEY WORDS: breakthrough pain (BTP), transdermal fentanyl.

INTRODUCTION

The pain is simultaneously a sensory experience, like sight and hearing, but it is also a feeling like fear or aggression. (Epicurus 300 B. C.) It is undoubtedly an unpleasant experience and in motivational sense it has a feature of a punishment. International Association for the Study of Pain (IASP) has issued an official definition of pain which states: "Pain is an unpleasant emotional and sensory experience linked to real or threatening tissue damage." Around 30-40% patients suffering from carcinoma already experience pain when they are diagnosed, while in terminal stage around 75-90% of patients experience pain, which says a lot about underestimation of carcinoma related pain, despite the information from palliative medicine facilities which states that in 95% of the cases this pain can be efficiently controlled (1). In 70% of the cases the pain is caused by the carcinoma itself and it occurs in a form of nociceptive or neuropathic carcinoma related pain (2). In 20 % of the cases the pain is caused by carcinoma treatment. Surgical interventions can cause nerve damage, chemotherapy releases cytokines which makes nociceptors susceptible to pain, radiotherapy leads to tissue fibrosis with nerve compression, and both chemotherapy and radiotherapy can cause painful mucositis (3). Empty bowel distension or distortion of capsule of solid organs cause visceral pain, in 5-10% of the cases the cause of pain is sudden loss of body weight, muscle spasms, immobilisation, decubitus and other. Palliative medicine sees pain as a complex problem and talks about so called total pain, comprised of four basic components: physical, psychological, social and spiritual, which ensures the treatment of symptoms, psychosocial and spiritual support for the patient and their family and it also ensures improved quality and complete care for the rest of their lives (4). The pain treatment has to be, as much as possible, causal, meaning that it has to treat the primal source of pain. When that is no longer possible, the "aggressive" treatment turns to palliative treatment. There are three causes which can lead to this: a) A patient has expressed his/her disapproval against the continuance of a specific oncological treatment; b) If a medical consilium finds that the aggressive measures would be futile and c) If a life prolongation would be unacceptable due to the experienced pain, psychological stress or other reasons. Those are at the same time the criteria for recognising the terminal stage of the illness when the principal of pain reduction gains a supremacy over the principle of life sustention. The estimate of pain intensity is based on patients' testimony and the usage of scales which are used

for an initial evaluation of pain but also for monitoring the effects of analgesic therapy. Inadequate pain evaluation could be a crucial factor of its inadequate treatment. Breakthrough pain (BTP) is a temporary sudden pain which is described as a subtype of an incidental pain which occurs over the usual persistent pain during the patients' opiate treatment (5). This sort of pain should be differed from poorly controlled basic pain, emergency cases pain and "crescendo" type of pain. When shooting pain occurs the basal pain is by definition, relatively stable and under control. According to Partenooy and Hagen definition BTP according to is intensity has to be strong to unbearable pain on basis of weak or middle intensity pain (6). They have also identified six characteristics that are relevant to understanding the BTP: The relation of breakthrough pain to fixed opiate dosage, time frames of BTP (duration, time of occurrence), and the cause of the appearance of BTP, possible predictability of its occurrence and its pathophysiology and etiology. The intensity of BTP differs and with 92% patients describe it as a very severe and intense pain (from 7-10 according to NRS) with fast, paroxysmal start (less than 3 minutes) and with average time of reaching the pain peak in less than 10 minutes, which also induces difficulties during the treatment (7). In 80-90% of the cases the duration is from 1 minute to 1 hour (usually between 15 and 30 minutes) and the average frequency are 4-7 painful episodes a day (8). In Great Britain BTP is an often used synonym for the "final failure" in pain treatment (9), while the Administrative Committee of European Association for palliative care (EACP) suggested the term "episodic pain" which they have divided into two groups with and without significant basal pain. BTP can occur spontaneously (in 27% of the cases) or it can be speeded up by activities such as movements, coughing, sitting down, touching (43% of the cases), distension of hollow organs (bowels, urethra) and psychosocial stimulus (10). In 17-30% of the cases BTP is related to inadequate analgesic treatment, whether the issue is sub dosage of analgesic or the interval between dosages that is too long, which leads to reduced concentration in plasma for example the opiates in the end of dosage interval and causes the increase of pain intensity or so called "deficiency in the final dose". The pain prevalence in patients suffering from cancer has been estimated to 50-70% among the patients that go through active treatment and in 70-80-95% of patients in the advanced stages of the disease (11). It is impossible to distinguish the mechanisms of spontaneous pain occurrence and breakthrough pain as well as occasional "pain flare" which can be seen in patients with or without carcino-

ma disease. The assumed causes of BTP in patients with cancer can be directly linked to nerve damage caused by a tumour or the anticancer treatment so that BTP can be classified as nociceptive, visceral nociceptive or neuropathic. Usually, the cause of breakthrough pain is related to bone pain (27%), local tumour invasion of soft tissue (21%) and the brachial plexus syndrome (9%). The basic mechanism of BTP is undetermined (12). From tumour cells and inflamed cells that are infiltrated into the tumour, the released prostaglandins (E1 and E2), proinflammatory cytokines (TNF, IL-1, IL-6), substance P, tumour growth factor activate nociceptors which spontaneously trigger and cause the painful stimulus (peripheral sensitization), and fast tumour growth can lead to compression and nerve damage, ischemia and direct proteolysis occurs(13). The prolonged triggering in neurons with C-receptors causes the release of glutamates which then activate N-methyl D-aspartate (NMDA) which causes the spinal cord neurons to become much more sensitive to all incoming stimuli, with astrocytic hypertrophy and the release of dynorphines deep in the laminae of vertebral arch, resulting in central sensitization (central activation of glial cells). Peripheral and central sensitization can increase the sense of pain and lead to the occurrence of non painful stimulation so that a soft touch or palpation can be recognised as severe pain (14). There are no clear guidelines, so the treatment depends on the type and the intensity of pain, and the individual experience of the therapist. The goal of the research was to determine the frequency, duration and causes of breakthrough pain (BTP), and its influence to cardiovascular system, in patients whose cancer pain was treated by transdermal fentanyl (TDF).

MATERIALS AND METHODS

A prospective study was conducted in a hospice for recumbent patients of the Centre for Palliative Care (hospice) University Clinical Centre Tuzla from October 2009 to December 2010. 33 patients in terminal stage of carcinoma (with finalised specific oncologic treatment) who had been hospitalised due to their ex-

cruciating pain (7-10 mark on numerical scale). The first day of treatment transdermal fentanyl in dosage of 25 µg was set. In the following 10 days the frequency, intensity, duration, time of occurrence and cause of breakthrough pain were recorded. BTP was reduced by "salvage doses" of oral morphine of 8 mg in a form of solution of morphine hydrochloride. On the fourth and seventh day the pain evaluation was conducted, so the dosage of transdermal fentanyl was gradually increased to 50 µg on the fourth day or 100 µg on the seventh day, if there were 2 or more pain breaches the previous day which required the salvage dose.

Following patients were excluded from the study: patients with cancer pain intensity 6 and lower (according to NRS scale); patients with allergies to heavy opiates; if they have used strong opiates before the tumour disease diagnosis or within the treatment of cancer pain before admittance to hospice; patients with active skin diseases which interferes with application of fentanyl patch; patients suffering from regurgitation which hinders the ability of applying the morphine orally; with distinct signs of respiratory, renal or liver insufficiency.

Statistical analysis was performed using the biomedical software known as MedCalc for Windows, version 9.4.2.0. For testing the repeated measurements of dependent samples, depending on the distribution of the variables, we used the even T-test, the Wilcoxon test and Mann-Whitney test. Statistical hypotheses were tested at the level of significance of $\alpha = 0,05$, that is, the difference between the samples was considered significant if $P < 0,05$.

RESULTS

Out of 33 patients of average age of 62, $45 \pm 10,61$, 19 (57,58 %) were male and 14 (42,42 %) were female. Based on medical documentation and examination of patients we gathered the information concerning the localization of the tumour and the occurrence of bone metastasis (Table 1).

		Topographic localization of tumour						
Tumour location		Head and neck		Thorax		Abdomen and pelvis		
Number of patients (%)		4 (12,1)		16 (48,5)		13 (39,4)		
		Clinical localization of the tumour and bone metastasis						
Primary		ORL	Skin	Lung	Breast	GI tract	Gynaec	Urology
Number of patients (%)		2 (6,1)	2 (6,1)	11 (33,3)	5 (15,1)	9 (27,2)	1 (3,0)	3 (9,1)
Bone metastasis	yes-19	1	1	7	4	3	0	3
	no-14	1	1	4	1	6	1	0

TABLE 1. Localization of tumour (topographic and clinical) and bone metastasis

Treatment	Oncological treatment							Sim. †
	OP*	CT [⊗]	R*	OP*+CT [⊗]	OP*+R*	CT [⊗] +R*	OP*+CT [⊗] +Z*	
Patients	3	1	1	9	1	6	10	2
%	9,1	3,0	3,0	27,3	3,0	18,2	30,3	6,1

Time frame from the diagnosis of tumour to terminal stage of the disease (TSD [⊕])				
Time frame from the dg of tumour to TSD	3 – 6 months	6 -12 months	12 – 36 months	36 – 72 months
Number of patients	8	10	13	2

OP* = operational; CT[⊗] = chemotherapy; R* = radiation; Sim. † = symptomatic; TSD[⊕] = terminal stage if the disease

TABLE 2. Oncological treatment and time frame from the diagnosis of tumour to terminal stage of the disease

With 24,2 % examined patients, the specific oncological treatment was completed (terminal stage of cancer disease), due to a personal decision or a decision of oncological consilium, 3 to 6 months following the pathohistological (PHD) diagnosis of the tumorous disease. Among the examined patients 30.3 % of them completed the specific oncological treatment after 6 to 12 months of treatment, after 1 to 3 years 39,4 % patients and 6,1 % of the patients after 36 to 72 months since the PHD diagnosis of tumorous disease (Table 2) Prior to the admission to Palliative care centre, 14 patients (42,4 %) have used only non opiate analgesics, 6 patients (18,2 %) used weak opiate analgesics and 13 patients (39,4 %) used a combination of weak opiates with non opiate analgesics. Upon the admission the mean pain intensity was $8,33 \pm 1,02$, which is statistically significantly higher compared to mean pain intensity after 10 days of treatment ($0,55 \pm 0,75$; $p < 0,0001$) (Table 3).

Already after 24 hour treatment of strong cancer pain by TD fentanyl statistically significant reduction of pain intensity occurs ($A_p < 0,0001$ compared to B) (Table 3). After stabilising the pain (by increasing the dosage of TD fentanyl if necessary) from fifth to tenth day of treatment there was no significant difference in the pain intensity, measured during restful period,

Day	Pain intensity through days	Day	Pain intensity through days	P
1	8,00(7,00-9,00) ^A	2	4,00(3,00-4,25) ^B	< 0,0001**
3	4,06 ± 1,89	4	2,06 ± 1,34	< 0,0001*
5	1,30 ± 1,21	6	1,72 ± 1,42	0,142*
7	1,12 ± 1,05	8	0,78 ± 0,99	0,085*
9	0,76 ± 1,00	10	0,55 ± 0,75	0,017*

*Presented as $\bar{x} \pm SD$ and **Median (Interquartile range); § rate past breakthrough pain

TABLE 3. the mean pain intensity in the order of days of treatment § outside the episodes of breakthrough pain (Figure 1). In 19 patients (56,6%) bone metastasis were verified based on previous medical documents, while 14 patients (42,4 %) did not have bone metastasis. (Chart 2) All three patients with urinary system tumour (2 with prostate tumour and 1 with urinary bladder tumour) had bone metastasis. Considering that the greatest number of examined patients had a tumorous lung disease (11 patients or 33,3%) bone metastasis were verified in 7 patients or 36,8 % of the total number of metastatic changes in all examined patients. It was established by examination that there are no statistically significant differences in pain intensity throughout the days of the treatment comparing the patients with and without bone metastasis (Table 4).

On the day of the admission in Palliative Care Centre 41 cases of breakthrough pain was recorded with 33 ex-

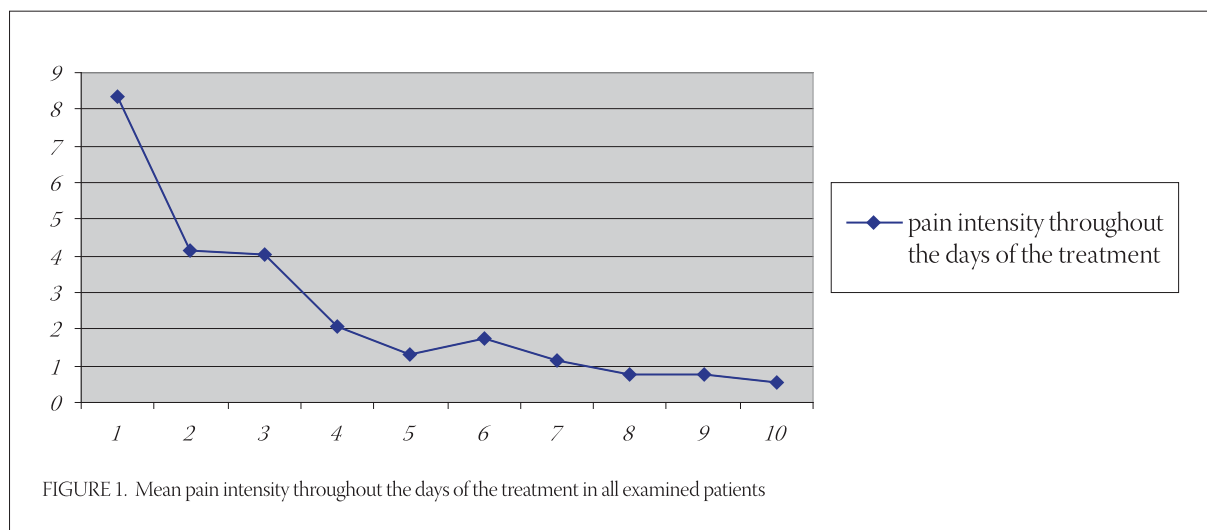


FIGURE 1. Mean pain intensity throughout the days of the treatment in all examined patients

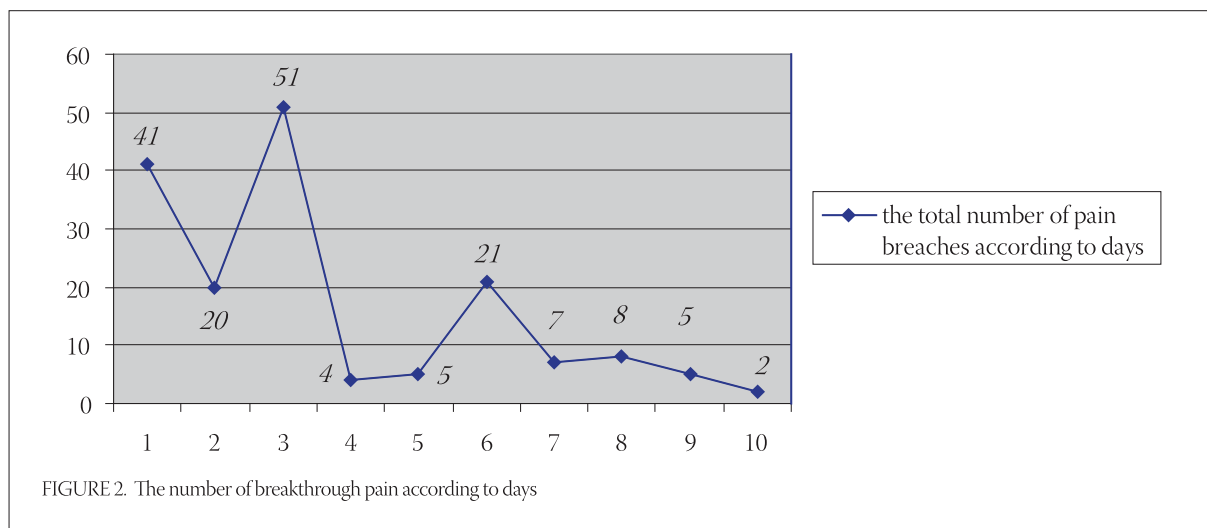


FIGURE 2. The number of breakthrough pain according to days

Day	Examined patients with bone metastasis†	Examined patients without bone metastasis	P
1	8,36 ± 1,06	8,31 ± 1,01	0,910*
2	4,00 (3,00 - 4,00)	4,00 (4,00 - 5,75)	0,155**
3	3,89 ± 1,85	4,28 ± 1,97	0,565*
4	2,11 ± 1,10	2,00 ± 1,66	0,828*
9	0,76 ± 1,00	10	0,55 ± 0,75

*Presented as $\bar{x} \pm SD$ and **Median (Interquartile range)

† Estimation of pain intensity during a restful period, aside the breakthrough pain

TABLE 4. Pain intensity in order of days with examined patients with and without the bone metastasis

aminated patients or $1,24 \% \pm 0,93$ breach of pain in mean per patient. On the second day the breakthrough pain was statistically significantly lower ($p = 0,0024$). The breakthrough pain was most frequent on the third day (51 or 31,0 % of 164 breakthrough pain in total) and also with 23 patients (69,7 %) there was a need to increase the dosage of fentanyl to 50µg, which was the optimal dosage for 18 examined patients until the tenth day of monitoring. With 2 patients there were 2 or more breakthrough pain on the sixth day so the dosage of

fentanyl was increased to 100 µg. Out of 23 patients whose dosage of transdermal fentanyl was increased (to 50 µg and then to 100 µg), 17 had bone metastasis while 6 of them didn't. The last day (10) of monitoring the mean number of breakthrough pain was statistically significantly lower in comparison to the day of admission to the Palliative care ($p < 0,0001$) (Figure 2).

Comparing the intervals (Figure 3), when pain evaluation and dosage correction of transdermal fentanyl was conducted (A = day 1-3; B = day 4 - 6 and C = day 7-10), the largest number of breakthrough pain (112 out of total of 164 or 68,3%) was recorded within the first three days upon the admission ($3,39 \pm 1,59$) which is statistically more significant than in the period from day 4 to day 6 ($p < 0,0001$). From seventh to tenth day of the treatment the number of breakthrough pain significantly lower compared to a period from day 4 to day 6 ($p < 0,0006$).

Within ten days of monitoring the mean frequency of breakthrough pain was $4,97 \pm 2,34$ per pa-

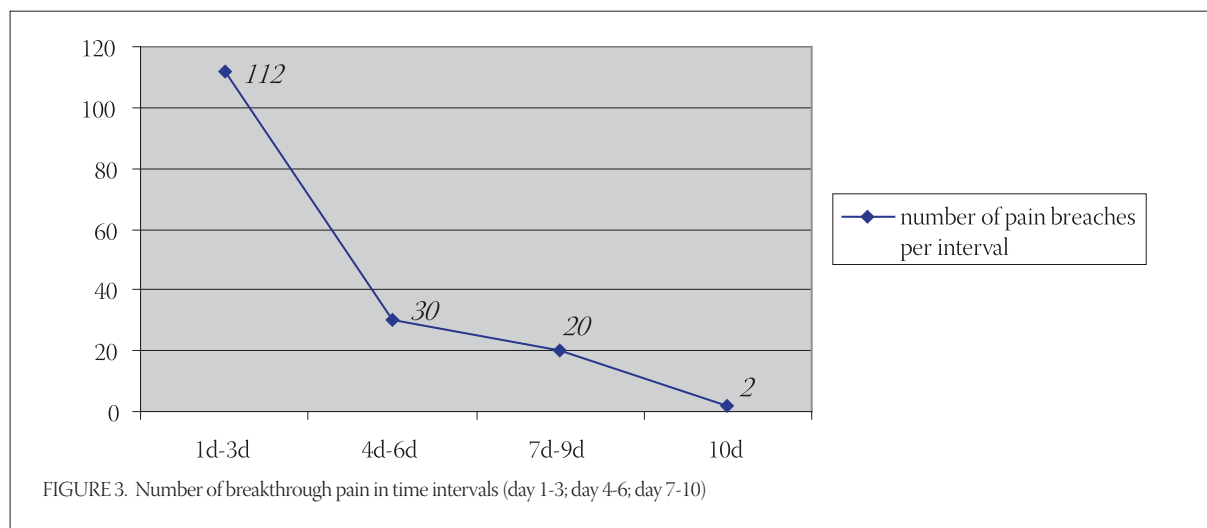


FIGURE 3. Number of breakthrough pain in time intervals (day 1-3; day 4-6; day 7-10)

Topographic localization	Head and neck	Thorax	Abdomen
The mean number of breakthrough pain per patient	4,25	4,81	5,38
The mean intensity of breakthrough pain *	9,26 ± 0,66 ^A	8,78 ± 1,07 ^B	8,80 ± 0,77 ^C

*Presented as $\bar{x} \pm SD$ ^Ap = 0,0032 compared to ^B; ^Ap = 0,011 compared to ^C; ^Bp = 0,931 compared to ^C.

TABLE 5. The frequency and intensity of breakthrough pain according to topographic localization of the tumour

tient. Most breakthrough pain (5,38 per patient) was registered with patients who had abdomen and pelvis (urinary, gynaecological and digestive system) tumours and the least were in patients with neck and head tumours (4,25 per patient). The mean intensity of breakthrough pain was 8,84 ± 0,92 which is statistically significantly stronger compared to pain upon the admission. (8,33 ± 1,02; p = 0,037), whereas the breakthrough pain was the most intense in patients with head and neck tumours (9,26 ± 0,66) (Table 5)

The lowest frequency of breakthrough pain occurred in time interval from 06 to 12 hours (13,4 %), and highest BTP was registered in the evening and at night (between 18:00 and 24:00 in 31,7 % of the cases and in 30,5 % of the cases in time interval from 24:00 to 06:00 h) with the duration less than 15 minutes in 65,2 % of the cases and only in 5,5 % of the breakthrough pain the pain lasted between 30 and 45 minutes. Cough, motions and other physical activities were the cause of breakthrough pain in 46,3 % of the examined patients. In 38,4 % of the cases the pain occurred spontaneously, while in 15,3 % of the cases the breakthrough pain is linked to occurrence of certain psychosocial incidents.

DISCUSSION

The mean intensity of pain, determined by a numeric scale, with our 33 patients on the first day of treatment was 8,33 ± 1,02. And on the fourth day of treatment by transdermal fentanyl it was significantly reduced to 2,06 ± 1,34 (p < 0,0001). In a study by L. Carenzo and associates (15) that was conducted with 40 patients with cancer pain, the mean value of pain on the first day reached 7,14 and after 72 hours it was reduced to 2,40, and on the seventh day of treatment by transdermal fentanyl it was reduced down to 2,07 (p = 0,002), with high percentage of contented patients (89 %) which is primarily linked to the simplicity of usage and fewer side effects. A study (16) conducted in China with 485 patients with strong cancer pain, re-

cords the radix of pain of 7,92. After applying TDF, on the first day already 86,3 % of the patients reported a pain reduction (of mean intensity 3,58; p < 0,001). In our study the mean frequency of breakthrough pain was 4,97 per patient during the monitoring time (range of 1 to 12; 0,497 breaches per patient a day), which speaks of underestimation, inadequate reporting and none distinguishing the existence of breakthrough pain. 68,3 % of pain breaches were registered within the first three days of the treatment (1,13 breaches per patient / per day). Cough, motions and other physical activities were the cause of pain breaches in 46,3 % of the examined patients. In 38,4 % of the cases the pain occurred spontaneously, while in 15,3 % of the cases the pain breach is linked to occurrence of certain psychosocial incidents. The mean duration of BTP was 17,3 ± 3,81 minutes, with the duration less than 15 minutes in 65,2 % of the cases and only in 5,5 % of the pain breaches the pain lasted between 30 and 45 minutes. A research conducted among the hospice patients in England (17) shows an mean of four pain breaches a day (range from 1 to 8) with mean duration of 35 minutes (range from 15 to 60), without any significant influence on vital parameters of the respiratory and cardiovascular system. Similar to our study, a research conducted in Spain (18) talks about underestimation and undistinguishing of BTP. Namely, with only 23 % of the patients with advanced carcinoma a breakthrough pain was reported. From the total of 397 patients, 163 (41 %) reported in total 244 episodes of breakthrough pain (1,5 per patient). The intensity of breakthrough pain was 7,3 according to NS, compared to our study which shows the mean BTP intensity of 8,84.

In our study, the episodes of breakthrough pain were treated by using fast acting morphine applied orally. One study conducted in Canada (19) and the other in Greece (20) recommend for the episodes of breakthrough pain to be treated by strong opiates (orally or subcutaneously by morphine, methadone, oral transmucosal fentanyl citrate). There are studies with different suggestions (21) which show that no titrational phase with fast acting opiate is needed, and that by using fentanyl patches as only analgesic, applying one day at the time titration method, the patients are provided with good analgesia with infrequent occurrence of breakthrough pain of low intensity. In the design of the study, the duration of monitoring should be prolonged and monitoring after the completed hospitalisation should be continued, also the effects of the transdermal fentanyl treatment should be compared to treatments with other strong opiates.

CONCLUSION

BTP is most frequent within the first three days of treatment by TDF. The optimal dosage of TDF enables a good pain control, regardless of the occurrence of bone metastasis. Also lower frequency and the intensity of pain are achieved. Optimal BTP control is linked specifically to personal experience. The ideal treatment of breakthrough pain would have such a pharmacokinetic profile that it would overlap the episodes of breakthrough pain (fast start and short duration) and it would have to be easy to administer for patients outside the hospital. The development of new pharmaceuticals and new ways of their application can be useful in reaching this goal. Transmucosal fentanyl citrate could be a promising solution for BTP control considering the quick absorption and the initiation of analgesia (5-10 minutes) and short duration of the effect.

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