Transmucosal in addition to transdermal fentanyl, administered in exacerbations of cancer pain, does not change the emotional status of patients

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ABSTRACT

Introduction: Opioids, regardless of the route of administration, are essential analgesics for the treatment of cancer pain. The transmucosal route of fentanyl administration is a relatively new but widely used technique.
Purpose: The authors attempted to assess the effectiveness of a submucosal dose of fentanyl, indicated for the control of breakthrough pain in patients who are on the transdermal fentanyl patch, and to evaluate the impact of both opioids on the emotional state of the patient.
Materials and methods: 48 patients were assigned to different analgesia groups, and the VAS pain scale and Beck Depression Inventory, before and after submucosal analgesia, were used to evaluate their pain.
Results: It has been shown that fentanyl provides dose-dependent analgesia. This analgesia is independent of the concentration of fentanyl in the blood serum. The method of administration of fentanyl has no effect on the level of depression, according to the BDI inventory. Furthermore, there is no statistically significant effect on the mood of the patient group based on the analgesia used.
Conclusions: Submucosal fentanyl added to the basic analgesic therapy is effective, well tolerated, and does not alter patient mood.
Key words: Breakthrough pain, submucosal fentanyl, cognitive processes, pain assessment, cancer pain therapy

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INTRODUCTION

Pain is one of the most-prevalent symptoms experienced by almost all patients [1-3]. Orally administered opioids for terminally ill patients are used preferentially, but other routes of administration are increasingly being employed [4, 5]. Transdermal (TTS Transdermal Therapeutic System) fentanyl is as effective as sustained-release oral morphine [6]. The low molecular weight (286 daltons) and high lipophilicity of fentanyl (reflected by a high octanol/water coefficient of 717) make it suitable for transdermal delivery [7, 8]. Steady cancer pain, well controlled by the standard therapy, can co-exist with acute brief episodes of pain that are poorly controlled. Breakthrough pain is usually managed with supplemental short-term opioid medications, given intravenously, subcutaneously, or orally [9]. The submucosal route of opioid administration is now under investigation [10]. Due to its lipophilicity, fentanyl is a suitable medication for buccal and sublingual administration. Transmucosal absorption of fentanyl into the blood stream is rapid, with peak plasma concentration achieved at about 20 minutes. Severe pain is hampered within 5 to 10 minutes following administration of the first dose [11].

Transdermal and transmucosal fentanyl produce the same adverse effects as other opioids, i.e., nausea, vomiting, constipation, and neurological symptoms such as drowsiness, sedation, vertigo, and sweating [12, 13]. Serious neurotoxic side effects of TTS fentanyl such as hallucinations, withdrawal, or convulsions were reported only rarely (0.2%, 0.1%, and 0.1% of 1,005 patients, respectively) [14]. Apart from good tolerance of fentanyl, dose-dependent deficits in pain effectiveness have been observed. This is important because the number of patients under fentanyl analgesia increases in cancer as well as in non-cancer chronic pain management [15].

In this study, we aimed to find out if a submucosal dose of fentanyl, indicated for the control of breakthrough pain, is effective in the treatment of pain in cancer patients. We also wanted to answer the question of whether the addition of submucosal fentanyl to TTS basal fentanyl therapy affects mood and cognition in patients.

MATERIALS AND METHODS

Thirty adult randomly selected patients (15 male, 15 female) with chronic cancer pain related to incurable malignancy and 18 people with cancer pain in good condition (12 male, 16 female) with week analgesic to control pain were included in the study (Tab.1). Not all cancer patients required opioid to control pain only part of them from study groups. Once tramadol (600-800mg/day) was insufficient, patients were switched to TTS fentanyl (25μg/h) and target to groups. For breakthrough pain oral (p.o.) paracetamol (500-1000 mg) or tramsmucosal fentanyl (50-100 μg) were given.

Table 1. Demographic characteristics.

Groups		**n**	**Age**	**SEM**
A	**C**	18	46.6	5.2
B	**F+P**	11	57.8	9.6
C	**F+F**	10	56.3	8.4
D	**F+TCAs**	9	52.5	6.1

The subjects were divided into 4 groups (9 -18 people in each):

A) (C) – control group (people with cancer, and without pain and any opioid drugs, patient on 1- step WHO leader);
B) (F+P) – cancer patients on TTS fentanyl (25-50μg/h) and paracetamol p.o. (500-1000 mg) as needed;
C) ($F+F_s$) – cancer patients on TTS fentanyl (25-50 μg/h) and transmucosal fentanyl (50-100 μg) as needed;
D) ($F+F_s$+TCAs) – cancer patients on TTS fentanyl (25-50 μg/h) and transmucosal fentanyl (50-100μg) according to the needs plus anxiolytic/antidepressant drugs - amitriptyline 25-59 mg/day.

In recruiting patients for this study we established criteria for age, sex, education and social status that allowed us to make up a fairly homogeneous groups untreated control. The exclusion criteria were: respiratory conditions causing documented or clinically recognized hypoxia, diabetes mellitus, epilepsy, psychosis, anxiety disorder, a history of cerebrovascular event, Cushing's syndrome, Addison's disease, dermatoses and collagen diseases, a clinically important gastrointestinal disease, myocardial infarction, any mitral or aortic valvular disease, renal insufficiency, trauma, fever, dehydration within the past 2 weeks, active treatment with hypnotics, sedatives, high dose hormone therapy, alcohol or drug abuse.

All patients were examined before and during fentanyl TTS analgesia (15-30 days). Blood samples were taken between 15-30 days after the start of TTS fentanyl treatment. Interviews and examinations were conducted by a trained psychologist or physician. All patients were in good or fairly good general conditions (according to Zubrod scale 0-2). All the examined patients were

able to communicate effectively. They were examined for the intensity of pain according to VAS scale, the quality of life and cognitive and emotional functions. The following set of tests was employed to test cognitive and emotional functions (16).

Beck Depression Inventory (BDI)

The BDI is a 21-item scale evaluating aspects of depressive symptomatology. Each item describes a specific behavioral manifestation of depression (e.g. sense of failure, mood, appetite, indecisiveness) and consists of a graded series of 4 to five self-evaluative statements. The statements are ranked to reflect the range of severity of the symptom from neutral to maximal severity. Each statement is assigned numerical values from 0-3 to indicate the degree of severity. The patients read statement in the category and select these which seem to fit best their mood during the last week.

Visual Analogue Pain Scale (VAS)

Estimation of pain intensity is a classic now and was used in a way described elsewhere. In this study, we used 100 point VAS scale. Where the 100 points on the scale stood for the worst pain, and 1 point was appointed for the best analgesia.

Serum analyses

The concentration of fentanyl in serum was determined by Gas Chromatography with mass selective detection [16]. Serum samples (1ml) were pipetted into 15ml test tubes. 0.5ml 1M NaOH was added to each tube, and the final volume was adjusted with water to 2 ml. After adding 6ml of methylenechloride the tubes were mixed on a rotary shaker for 20 minutes. The samples were centrifuged at 3000g for 10 minutes. The organic phase was transferred to clean test tubes and evaporated to dryness under a gentle stream of nitrogen. The residues were reconstituted with 100µl of toluene. 2µl samples were injected into a Gas Chromatograph (GC). Fentanyl was analyzed using a Perkin-Elmer Autosystem XL with TurboMass detector. The samples were injected in the split mode. An Elite-5MS column (30m x 0.25mm I.D.x 1um film thickness) was used for fentanyl separation. GC conditions were as follows: Injection port temperature 250°C, initial oven temperature 200°C, ramped to 320°C. at a rate of 25°C/min. Helium was used as the carrier gas with flow 1ml/min. Transfer line temperature was stated at 300°C, using the electron-impact (EI+) ionization mode. Fentanyl was quantitated by selected ion monitoring (SIM) mode [17]. Concentration of fentanyl was read from calibration curve (Fig. 1).

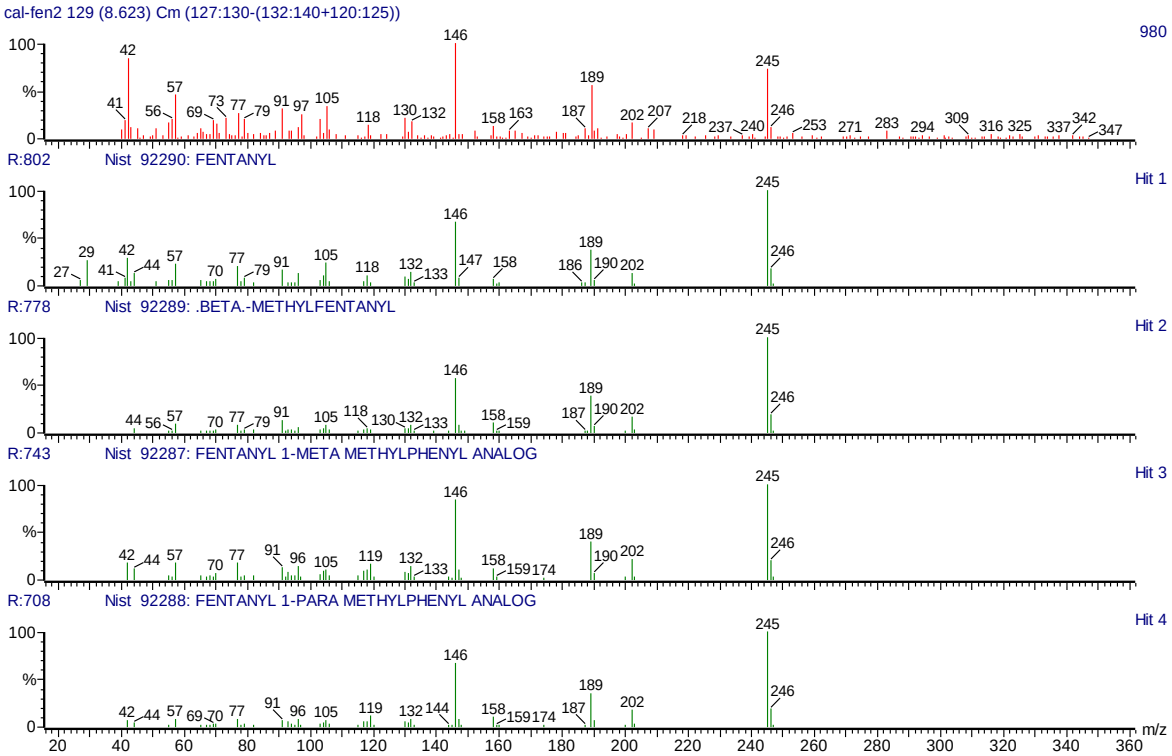

Figure 1. Analysis serum concentration of fentanyl were conducted SIM metod: /Selected Ion Monitoring/ (m/z 42,105,146,189,245,279) picture show ratio mass to charge ratio characteristic of fentanyl - test sample retention time of fentanyl - 8.13 min.

Statistical analysis

For statistical evaluation of the data, one-way analysis of variance (ANOVA) was employed. If the outcome was significant, the Newman-Keuls test was used to distinguish between-group differences. F-ratios, degrees of freedom and P-values are reported only for significant differences. In all comparisons between particular groups a probability of $p<0.05$ or less was considered significant.

Ethics

The Senate Ethics Commission, Medical University of Białystok approved the protocol of this study. Patients were informed of the purpose of the examinations and gave their written consent. Neither patients nor control subjects received money for their participation.

RESULTS

Not all patients finished this study, from the examined study group two patients died and one patient not finished study because he was hospitalized. From the control group, seven patients were hospitalized for reasons of progress cancer and necessity of radiotherapy and chemotherapy. Median age for cancer patients was 56.3 (range 52.3-66.1), for no cancer pain patient 46.6 (range 43.1-48.3) (Fig. 1).

Serum concentration of fentanyl depends on fentanyl transdermal doses, and no significant differences were observed between patient groups. Analysis was conducted from mass to charge ratio characteristic of fentanyl, and retention time of fentanyl were 8.13 min (Fig. 2).

Table 2. Serum concentration of the fentanyl patients with fentanyl basic and trans-mucosal analgesia, 1-5 and 8 number subject of 9 patient from C group (F+F) and serum concentration of fentanyl and amitriptyline 6,7,9 to 11 patient number, D group (F+TCAs). No differences between serum levels of fentanyl were observed.

Patient no	Groups	Doses	ct ng/ml
1	F+F	50	0.71
2	F+F	75	0.76
3	F+F	50	0.8
4	F+F	75	-
5	F+F	200	1.32
6	F+TCAs	200	1.57
7	F+TCAs	50	0.84
8	F+F	25	0.51
9	F+TCAs	150	1.33
10	F+TCAs	50	1
11	F+TCAs	150	1.86

Only 10 subjects had properly blood samples taken. Analysis of level fentanyl serum data not show differences between basic fentanyl level - transdermal with extra dose trans mucosal fentanyl compare to fentanyl and antidepressant drugs group. Evaluation on pain at rest and on movement decreased significantly from baseline to final assessment (mean scores 33.4; 31.3; 29.2 and 30.1 respectively, at baseline, falling to 7; 15.6; 10.5; 9 point on 100 point vas scale (Fig. 3).

Table 3. Table shows evaluation on pain at rest and on movement Visual Analog Scale (VAS, 1-100).

Group	N	VAS before TTS Analgesia		VAS 21th day of TTS Analgesia		
		Mean VAS	SEM	Mean VAS	SEM	(p)
C	11	33.4	7.6	7.1	1.9	2.5
F+P	9	31.3	6.2	15.6	2.1	0.8
F+F	9	29.2	7.4	10.5	2.0	0.2
F+TCAs	9	30.1	8.7	9	5.2	0.9

Additional transmucosal fentanyl also had no significant effect on emotional processes (mean scores 15.0; 16, 1; 9.2 and 10.74, respectively, at baseline, falling to 12.5; 15.3; 9.4; 9.7 point on 100 point VAS scale group with antidepressant and/or anxiolytic drugs showed a slight decrease in the number of point in Back Depression Inventory but no statistically significant effect was noted of any of the employed types of anesthesia on the mood of patients (Tab. 4).

Table 4. Data of patients who completed the questionnaire of emotional status in Beck Depression Inventory (BDI).

			5 day before analgesia		7 day bfter analgesia		
Name of groups		n	Mean	SEM	Mean	SEM	(p)
A	**C**	9	15.0	3.5	12.5	3.5	-
B	**F+P**	9	16.1	2.9	15.3	3.2	-
C	**F+F**	10	9.2	2.5	9.4	2.4	0.3
D	**F+TCAs**	9	10.7	2.9	9.7	2.1	-

A - control group without analgesia, B - patients who use TTS fentanyl 25-50 μg/h p.c. and paracetamol p.o. according to the level of pain, C - patients with TTS and additionally given fentanyl 50-100 μg per os according to the needs, D - patients who take anxiolytic and antidepressants

therapy together with TTS and additionally given fentanyl 50-100 μg per os according to the needs.

Quality of life improved significantly, and 61% of patients were satisfied with the treatment. Ability to undergo physical therapy improved significantly. (Results are not shown)

DISCUSSION

The study of effects after TTS fentanyl administration was performed in cancer patients with measured plasma fentanyl concentrations [16]. All patients were treated by transdermal fentanyl for two months. Some patients took an antidepressant and/or anxiolytic drugs in addition to fentanyl. Study shows that analgesia is effective, and no change in depression was observed. Plasma fentanyl concentration range between 0.51 and 1.86 ng/mL was access in fentanyl and fentanyl and adjutants groups. A battery of tasks was administered at each patient's groups. Compare to above data in group with „alone" fentanyl analgesia at the plasma fentanyl concentration of 1.86 ng/mL, we found the same level of analgesia according to VAS scale. No change in the mental status assessing Back depression scale in all TTS fentanyl groups compared with control. There is some literature data show change mental status after fentanyl analgesia and some report of antinociceptive effects of fentanyl. We don't observe in the study this phenomenon [17,18, 19].
Population of fentanyl target humans improves every year [20,21]. Continuous epidural, intravenous pomp infusions and transdermal administered preparations are wide used to relieve pain [22,23]. Fentanyl is commonly administered to conscious cancer and non cancer older patients as an analgesic agent but the adverse effect in humans is not clear [16,24]. It seems to be important to give save analgesia in generally healthy senior with mild psychomotor dysfunction [26] The transdermal and transmucosal route results in relatively low concentrations of fentanyl [27]. The new and not popular form of breakthrough pain treatment is a trans-mucosal route of fentanyl. This kind of administration of fentanyl is particularly useful in severe cancer pain [23]. Trans-mucosal fentanyl or oral paracetamol, according to the individual patient's need, were given as breakthrough pain treatment in our patients and all of them had a good tolerance of extra dose opioid and also had a good pain relief.

Extra doses of transmucosal fentanyl (without any adjuvant drugs) did not change emotional status and quality of life. Patients from all groups showed the same points of Chopkin's and Beck's depression scales. There is some theoretical fentanyl possibility to change emotional and mental patient status [28]. Yoshida demonstrated an increases dopamine release from nucleus accumbens due to fentanyl analgesia, and Mortazavi and Sakai show in vivo inhibit an acetylcholine release in some modulating regions in the rat brain [29, 30].

On the other hand, it is widely observed the increased therapeutic use of opioids by the chronic non cancer pain patients, especially with chronic back pain. The use of opioids improves the quality of life, but the degree of illness acceptance may influence the therapeutic process and may change mood status [31]. Assess the impact of opioid action in the state mood patients with non cancer pain should be investigated in detail. In the study, visual analog scale (VAS) measures of mental and physical sedation were significantly affected by fentanyl, but euphoria was not demonstrable and mental statuses were not changed. None subjects receiving fentanyl experienced severe nausea and emesis. Pain relief was good and very good (according to 1-100 point VAS scale).

CONCLUSIONS

We suggest the transdermal fentanyl analgesia is save procedures in the conscious adult patients. Occasionally, trans-mucosal extra dose of fentanyl does not change patient cognitive emotional status.

Conflicts of interest
There was no conflict of interest in this study.

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