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Efficacy and safety of TTS fentanyl given directly after tramadol to patients with cancer related pain (based on FEN-POL-2 trial)

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The main purpose of the trial was to investigate the clinical efficacy and safety of TTS fentanyl administered over 28 days to patients naive to strong opioids, treated over the past 3 days prior to entering the study with the maximal (400 mg) daily dose of tramadol. Seventy two patients were included in the study, all of them suffering from advanced cancer- related pain. All patients started with the lowest availabe dose of fentanyl (delivery rate 25 μg/hr . If analgesia was insufficient, the patients were given a strong opioid (5 mg of immediate-release oral morphine) or a non- opioid analgesic as 'rescue' medication. Pain intensity was evaluated by means of the Visual Analoque Scale (VAS) and the Verbal Rating Scale (VRS). Sixty four patients were eligible for analysis. During the study 18 patients continued with 25 μg/hr, and the remaining was administered a higher dose. The maximum dose was 150 μg/hr (2 patients). At the termination of the trial 45/64 (72%) patients had no pain or slight pain, 15/64 (22%) had moderate pain and 4/64 (6%) experienced strong or very strong pain (VRS). At the end of the trial in 51/64 (79%) pts pain control was good to excellent (in an overall assesment of pain treatment). Clinically relevant respiratory depression was not observed. The following side effects of opioids were observed: nausea(N=3), vomiting (N=3), constipation (N=2) and sweating (N=1). Transdermal fentanyl proved to be an effective and safe analgesic in the treatment of cancer- related pain in patients naive to strong opioids.

Ocena efektywności i bezpieczeństwa stosowania TTS fentanylu bezpośrednio po tramadolu, u pacjentów z bólem pochodzenia nowotworowego (na podstawie badania FEN-POL-2 trial)

Celem badania była ocena skuteczności i bezpieczeństwa stosowania TTS fentanylu u chorych z bólem nowotworowym, którzy poprzednio nie otrzymywali silnych opioidów. Do badania włączono 72 pacjentów, leczonych przez ostatnie 3 dni tramadolem w dawce 400 mg na dobę z niedostatecznym efektem przeciwbólowym. Natężenie bólu oceniano za pomocą Wizualnej Skali Analogowej (VAS) oraz Słownej Skali Oceny Bólu (VRS). U wszystkich badanych stosowanie TTS fentanylu rozpoczęto od dawki 25 μg/godz., a w razie wystąpienia bólu przebijającego podawano 5 mg roztworu wodnego szybko działającej morfiny lub nie opioidowe leki przeciwbólowe. Podczas badania dawkę początkową TTS fentanylu utrzymano u 18 chorych, pozostali wymagali zwiększenia dawek. Maksymalna dawka wynosiła 150 μg/godz. i była stosowana u 2 pacjentów. Trwające 28 dni badanie ukończyło 64 chorych. W ostatnim dniu badania 45/64 (72%) chorych zgłaszało brak bólu lub ból o nieznacznym nasileniu, 15/64 (22%) ból o średnim natężeniu, a 4/64 (6%) ból silny lub bardzo silny wg VRS. W trakcie badania wystąpiły następujące objawy uboczne: nudności (N=3), wymioty (N=3), zaparcie stolca (N=2) i wzmożona potliwość (N=1), u żadnego z badanych nie pojawiły się objawy depresji oddechowej. TTS fentanyl okazał się skutecznym i bezpiecznym środkiem w leczeniu bólu nowotworowego u pacjentów nie pobierających wcześniej silnych opioidów.

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Słowa kluczowe: ból nowotworowy, przezskórny fentanyl, tramadol, objawy uboczne

Introduction

The prevalence of pain has been estimated to occur in 30--50% patients undergoing oncological treatment and in 80-90% of palliative care patients [1]. WHO has introduced a 3-step analgesic ladder to give structure to the treatment of cancer pain. Pharmacotherapy carried out according to the WHO outlines is sufficient in 80-90% of cancer pain [2]. Most of the patients (up to 70%) need strong opioids to obtain good pain control [3, 4]. The changes in blood concetration caused by oral, im, and iv bolus administered drugs, may be accompanied by clinical responses fluctuating between inadequate analgesia and unwanted side effects. It is important to prevent and treat the common side effects of opioids, especially nausea, vomiting and constipation [5]. However there still exists a need for an efficient, safe and convenient analgesic agent for cancer- releted pain. Transdermal fentanyl introduced in 1992 provides continuous opioid delivery without the need for special equipment. The transcutanous system provides constant release of the opioid for up to 72 hours [6-8]. The simplicity of TTS fentanyl administration allows freedom to maintain a relatively normal lifestyle. Some studies show that TTS fentanyl causes less side effects (especially constipation), than morphine [9]. Many studies have been conducted to evaluate the safety and efficacy of TTS fentanyl in patients treated previosly with other strong opioids [10, 11]. To provide adequate analgesia sometimes we have to move directly from step 1 to step 3 of the analgesic ladder. This trial was designed to investigate the efficacy and safety of TTS fentanyl as first line treatment on stage III of the WHO ladder. in strong opioid naive patients treated previously with up to the maximal daily dose of tramadol.

Methods

The trial was performed in 6 oncology centres in Poland. The main purpose was to investigate the clinical efficacy and safety of TTS fentanyl given over the period of 28 days to strong opioid naive patients, treated over the last 3 days prior to entering the study with the maximal (400 mg) daily dose of tramadol. All of them required strong opioids for pain management. 6 (8%) patients suffered, only slight pain according to VRS, but were included, because they demanded a better pain control. Sixty six (92%) pts had moderate to very strong pain despite taking 400mg of tramadol a day.

The main objectives of this trial consist of the assessment of: pain control, the performance status using the Karnofsky and ECOG scale, the incidence and severity of adverse events (nausea, vomiting, constipation, dyspnoea, cough) and the convenience of the use of the patches. The severity of pain experienced during both the day and night was evaluated by means of the VAS (Visual Analoque Scale) and the VRS (Verbal Rating Scale). An overall assessment of the pain treatment was performed using 4-point scale (excellent, good, fair, poor) on day 1 and day 28. As in most studies with patients with cancer pain, an open design has been chosen for this study, and the recruitment of patients was directed by the centres without randomisation. Inclusion criteria were: histologically confirmed malignancy that is not amenable to curative therapy at presentation, pain caused by malignant disease, strong opioid naive patients, who require analgesia according to step 3 of WHO analgesic ladder, previous treatment with up to 400 mg of tramadol, age 18 years or more, estimated survival of at least 3 months, ability to communicate, in women – adequate contraception in case of childbearing age, the ability to read and sign informed consent. Exclusion criteria were: a history of drug allergy to opioids, a history of narcotic abuse prior to the diagnosis of cancer, active skin disease precluding application of the transdermal system, radiation therapy for any painful sites within 7 days of entering the study, participation in an investigational drug trial during 30 days prior to the selection, changes in hormonal and/or cytostatic medication within the 7 days preceding entry into the study, serum bilirubin level >2.0 mg/dl, serum creatinine level >2.0 mg/dl, any co-existing medical condition that is likely to interfere with the study procedures.

TTS fentanyl was started with the lowest available dose (25 μg/h). A dose increase was allowed, if needed, every third day. Due to the pharmacokinetics of the patch, sufficient analgesic fentanyl concentration is reached within first 24 hours. For that reason, for the first 12-24 hours, the therapy of tramadol should be continued with the same dose as previously. If, after 24 hours of TTS fentanyl, analgesia is not sufficient, rescue medication (5 mg immediate-release oral morphine or non-opioid drug) must be administered. The flow chart showing trial phases and timing of treatment and assessments is given in Table I.

Results

Seventy two patients (45 men and 27 women) were included in the study. Mean age was 58 years (28-80 yrs.).

All patients reported cancer related pain. Primary tumour localisations are listed in Table II. Losses from observation: 3 deaths caused by disease progression, 4 cases of withdrawn consent (1 (SAEs) – day 2, nausea, vomiting, dizziness; 1 – day 4, poor pain control; 1 – day 10, no reason given; 1 – day 26, progressive weakness). One patient stopped the treatment prematurely because of Serious Adverse Experience (SAE) (doubtful relation to treatment medication) and died 7 days later. Sixty four patients completed the study.

Transdermal fentanyl dose and analgesic effect

All patients started with the lowest available dose of fentanyl (delivery rate 25 μg per hour). The dose had to be increased in 46 patients. Dose stabilisation was observed after on average 3 weeks of treatment. The maximum dose reached 150 μg/hr on day 22.

The severity of pain experienced during the day and the night was evaluated by means of VAS and VRS. If analgesia was insufficient, patients were given a strong opioid (5 mg of immediate-release oral morphine) or non-opioid analgesic as rescue medication (Figure 2). The most frequently used non-opioid drugs were: keto-

Table I. Flow chart

Visit nr	1	2					3				4
Visit day	1	2					16				28
Telephone contact			4	7	10	13		19	22	25	
Performance status	X						X				X
Concomitant medication	X	X					X				X
Determination of dose of TTS-fentanyl	X	X					X				X
Overall evaluation of pain treatment	X	X	X	X	X	X	X	X	X	X	
Disease progression											X
Evaluation of gastrointestinal disturbances	X						X				X
Patient's preference											X
Convenience of use of the patches											X
Adverse experiences											X
Rescue medication		X	X	X	X	X	X	X	X	X	X
VAS		X	X	X	X	X	X	X	X	X	X
Evaluation of dyspnoea and cough	X						X				X
Patient (diary)	Daily										
Nausea and vomiting											
VAS											
VRS											
Resque medication: (dose and freq./24h											
Adverse events											

Table II. Primary tumors

Primary tumors	Number of patients
Melanoma	2
Head and neck ca	3
Adenocarcinoma (nonsp.)	2
Ovarian ca	4
Ovarian and pancreatic ca	1
Colon ca	6
Kidney ca	2
Lymphoma	1
Lung and bone metastases of unknow origin	1
Urinary bladder ca	1
Lung ca	32
Breast ca	9
Carcinoid	1
Retroperitoneal space ca	1
Cervix ca	4
Myeloma	1
Stomach ca	1

profen (19 pts), naproxen sodium (1 pt), diclofenac (2 pts), metamizol sodium (2 pts), paracetamol (2 pts) and papaverinum (2 pts).

At the end of the trial 45/64 (72%) pts experienced no pain or slight pain, 15/64 (22%) pts had moderate pain and 4/64 (6%) pts strong or very strong pain (VRS).

We noted an increase in the number of patients who reported no pain or slight pain (VRS) on day 28 as com-

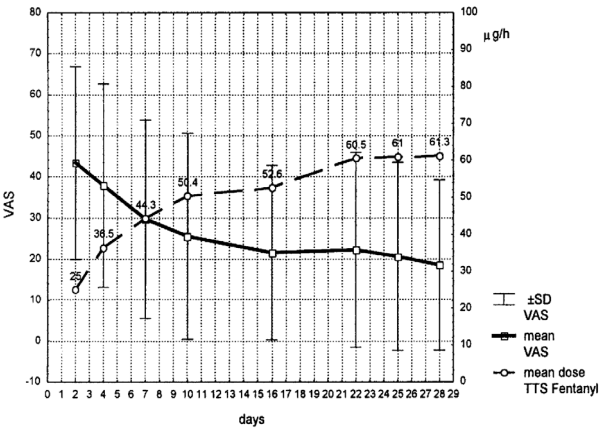

Figure 1. Average pain control (VAS) and mean transdermal fentanyl dose during the trial

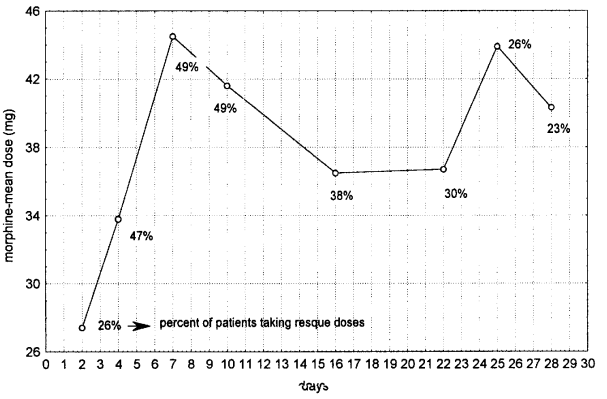

Figure 2. Average morphine consumption (rescue medication) on respective days of the treatment

pared to day 1 (see Table III). On day 28 we also noted a significantly lower number of patients reporting moderate, strong or very severe pain as compared to day 1. Total assessment of the treatment at the end of the trial was excellent in 15/64 (23%) pts, good in 36/64 (56%) pts, fair in 9/64 (14%) pts and poor in 4/64 (6%) pts. Mean time needed to obtain good pain control (VAS <30mm) was 7 days (Figure 1).

Table III. Pain assessment (VRS) on day 1 (baseline data) and day 28

VRS	day 1	day 28
no pain or slight pain	6/72 (8%)	45/64 (72%)
moderate pain	27/72 (37%)	15/64 (22%)
strong or very strong	39/72 (55%)	4/64 (6%)

Nausea and vomiting

All patients were given metoclopramide (30 mg/daily) to prevent nausea and vomiting. The severity of nausea was evaluated once daily using a 4-point scale and was recorded in the patients' diary each day. Absence of nausea was reported by 53/72 (75%) patients, mild nausea by 15/72 (20%), moderate by 3/72 (4%) and severe by 1/72 (1%) at the beginning of the trial, versus (respectively) 50/64 (78%), 11/64 (17%), 3/64 (5%) and 0/64 (0%) on day 28. Also the frequency of vomiting was recorded. 9/72 (13%) pts reported vomiting at the beginning and only 2/64 (3%) on day 28.

Dyspnoea and cough

The severity of dyspnoea and cough was evaluated according to a 4-point scale and recorded in the patients' diary each day. On the first day absence of dyspnoea reported 46/72 (64%) patients, mild dyspnoea 18/72 (25%), moderate 7/72 (10%), severe 1/72 (1%) and respectively 42/64 (66%), 15/64 (23%), 5/64 (8%) and 2/64 (3%) on day 28. Cough was evaluated according to the same scale. On the first day absence of cough was reported by 47/72 (66%) patients, mild cough 19/72 (26%), moderate 5/72 (7%), severe 1/72 (1%) and respectively 44/64 (69%), 16/64 (25%), 4/64 (6%) and 0/64 (0%) on day 28.

Gastrointestinal disturbances

The effects on the gastrointestinal tract were assessed by evaluating the number, the consistency and the passage of stools, the presence of abdominal pain and bloating, and the use of laxatives at each visit.

18/72 patients (25%) reported abdominal pain on day 1 and 10/64 (16%) on day 28. 23/72 patients (32%) reported the use of laxatives on day 1 and 23/64 (37%) on day 28. 37/64 (58%) patients described their stool as normal on day 28, as compared to 33/72 (46%) on day 1, constipated stools were reported by 39/72 (54%) patients on day 1 and 27/64 (42%) on day 28. The stool was "not at all" or "a little of the time" difficult to pass for 28/72 (72%) patients on day 1 and 21/64 (78%) on day 28. Stools passed on less than 3 days/week on the first day were reported by 17/72 (44%) patients versus 11/64 (41%) on day 28.

General condition

The patients' general condition was recorded using the Karnofsky performance status scale and the ECOG scale before treatment (day 1), on day 16 and 28. The average Karnofsky performance status score was 75 % before the first medication and 74 % on day 28. According to ECOG scale the patients' performance status was slightly worse at the end of the treatment in comparison to the score obtained at the beginning. This could have been due to disease progression.

Adverse events

During 28 days of this trial, 3 patients died as a consequence of advanced cancer. One patient stopped the treatment prematurely, because of serious AEs (dyspnoea, pain in the abdomen and in the chest) and died 7 days later. There was doubtful relation to the trial medication It was a patient with inoperable, advanced pancreatic and ovarian cancer. The patient reported increasing dyspnoea and pain in her back on 25 day of Durogesic treatment. She was admitted to the hospital the next day, due to severe dyspnoea and pain in her chest and abdomen. The X-ray of her chest revealed multiple metastases to the lungs. Durogesic treatment was stopped on the day of addmission, morphine and fentanyl iv were implemented instead. The patient died 7 days later due to cancer progression.

One patient reported vomiting, dizziness, nausea and another patient reported dyspnoea – these AEs were possibly related to the trial medication.

The AEs regarded as probably, or very likely related to transdermal fentanyl treatment were: nausea (N=3), vomiting (N=3), constipation (N=2) and sweating (N=1) and were observed in 7 patients.

Discussion

Most of the studies on transdermal fentanyl have included strong opioid tolerant patients, and presented a change to TTS fentanyl, after a stabilisation phase with either a short acting strong opioid or intravenous fentanyl. Some recent trials had included strong opioid naive patients with insufficient pain control [12]. These studies have shown, that both opioid naive and opioid tolerant patients with chronic cancer pain requiring strong opioids may be treated with TTS fentanyl without a prior stabilisation phase. The need of a pain stabilisation phase with morphine can therefore be questioned, and as a consequence of these studies patients with stabilised and unstabilised pain, as well as opioid naive patients, could therefo-

re be switched immediately to TTS fentanyl. A dose titration must, however, be performed under close monitoring. In most studies, adequate relief of breaktrough pain was obtained by adding oral morphine, as rescue medication. In our trial rescue dose was relatively low (5 mg immediate-release morphine), because we did not want the side effects of opioids interfere with TTS fentanyl side effects. No pain or slight pain according to VRS was reached in 72% patients on day 28. Similar good effects of TTS fentanyl used in 14 codeine treated, and 14 strong opioid naive patients were noticed in a recent study [12]. Vielvoye-Kerkmeer et al. reached a good and very good analgesic effect in 68% of patients, constipation occurred in 3 (11%) patients. All patients in the study started with 25 ug/h TTS fentanyl, but the dose was sufficient in only 5 (18%) patients, and respectively in 18 (28%) in our study. Rescue doses in our study were used more frequently during the few first days, and the highest average morphine consumption was noticed on day 7, and then on day 25. More than 66% of patients needed dose increasing. The dose was increased to 50ug/h in 25 patients and to 75ug/h in 4 patients on day 4. The mean time needed to obtain good pain control (VAS <30mm) was approximately 7 days. The initial dose of TTS fentanyl in our trial was 25ug/h, no matter how strong the pain was. Higher initial doses of TTS fentanyl in some cases, and higher rescue doses of morphine would probably shorten the time before good pain control is obtained. According to Twycross good pain control on morphine usually is obtained after 3 to 5 days (at rest), and after 3 to 7 days (on movement) (14).

Constipation existed in 39/72 (54%) patients on tramadol (the first day of the trial) and in 27/64 (42%) on the last day. Investigators observed only 2/64 (3%) cases of „de novo" occured constipation during the trial and they reported them as AEs associated with the study medication. Rescue doses of morphine could have been responsible for constipation in some cases. Many studies have proven that TTS fentanyl causes less constipation then morphine [9, 10], which can be due to higher lipofility of fentanyl, which leads to faster penetration to the CNS and lower peripheral effects. We observed a decrease in nausea from 25% of patients on day 1 to 22% on day 28; and in vomiting – from 13% to 3%, respectively.

Conclusion

A global assessment of the pain treatment with TTS fentanyl was excellent in 15/64 (23%) pts, good in 36/64 (56%), fair in 9/64 (14%) and poor in 4/64 (6%) pts.

In this trial transdermal fentanyl proved to be a good and safe analgesic agent for the first line treatment of moderate to severe pain in strong opioid naive patients. Clinically relevant respiratory depression was not found. Constipation occurred in 2 (3%) patients. We did not observe serious AEs related to the trial medication. Overall, the treatment was appreciated and well tolerated by the patients. TTS fentanyl, (especially equivalent doses of fentanyl and tramadol) in patients naive to strong opioids needs further investigation.

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