NOWOTWORY 2001/ tom 51
Zeszyt 3 / 257–266

Analgesic efficacy and side effects of oral tramadol and morphine administered orally in the treatment of cancer pain

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Aims of the study. To assess the analgesic efficacy and side effects of tramadol and equianalgesic doses of morphine and to assess the quality of life (QL) in patients suffering from cancer pain and to establish equianalgesic doses of oral tramadol and morphine.

Patients and methods. Fourty opioid-naive patients with moderate, strong or very strong cancer pain (verbal scale) or at least 45 mm on VAS scale, were treated with tramadol (20 patients) or morphine (20 patients). During the first 7 days the pain was stabilised by the use of immediate release forms of tramadol (drops, capsules) or morphine (water solution). After 7 days, if a satisfactory pain relief was achieved and appropriate daily doses were applied (tramadol 150-600 mg, morphine 20-200 mg) patients were switched to controlled release forms of tramadol – Tramal Long (Retard) tablets – or sustained release morphine (MST Continus tablets or M-eslon capsules) for 28 days. QL was assessed by QLQ C 30 questionnaire. Pain intensity was appraised by VAS and verbal scale, side effects by verbal scale.

Results. The duration of treatment was 3-310 (mean 87.15±78.23) days for Tramal Retard and 5-502 (mean 100.05±102.67) days for morphine MST Continus and M-eslon. Daily doses were as follows: 200- 600 (mean 322.22±116.60) mg for tramadol and 20-270 (123.5±78.15) mg for morphine. Satisfactory analgesia was achieved in both groups. However, in patients with neuropathic pain better analgesic effect was noted in the morphine group (significant difference in VAS scale after first week of the treatment). 80% of patients in both groups preferred the treatment with controlled release forms of tramadol and morphine. The treatment was well tolerated, 17 patients in tramadol group and 18 in morphine group completed the study. More side effects were noted in morphine group, however significant differences appeared only in drowsiness, difficulties in passing urine, sweating and dizziness intensity. QL results revealed better global QL and less fatigue after 35 days of the tramadol treatment.

Conclusions. Tramadol and equianalgesic doses of morphine (up to 270 mg/day) in immediate and controlled release forms are effective in the treatment of different types of moderate and severe cancer pain. Tramadol is less effective in patients with neuropathic pain. Both drugs can be safely used at home. Better global QL and less fatigue was observed after 35 days of the tramadol treatment. Tramadol is recommended in patients with moderate pain (VAS 30-54 mm) and morphine in patients with severe and very severe pain (VAS >54 mm). Equianalgesic doses of tramadol and morphine administered orally are 4:1.

Ocena przydatności analgetycznej i objawów ubocznych tramadolu i morfiny, podawanych drogą doustną, w leczeniu bólu nowotworowego

Cele badania. Ocena analgezji, objawów ubocznych i jakości życia (JŻ) podczas leczenia tramadolem i ekwiwalentnymi dawkami morfiny, u chorych z bólem nowotworowym oraz ustalenie równoważnych dawek obu leków, podawanych drogą doustną.

Badani chorzy i metody. 40 chorym z bólem nowotworowym o umiarkowanym, silnym lub bardzo silnym natężeniu wg skali słownej lub przynajmniej 45 mm wg skali VAS, którzy uprzednio nie byli leczeni analgetykami opioidowymi, w ramach otwartego, randomizowanego, równoległego, prospektywnego badania, podawano tramadol (20 chorych) lub morfinę (20 chorych). Przez pierwsze 7 dni chorzy otrzymywali tramadol (krople lub kapsułki) lub morfinę (roztwór wodny) o natychmiastowym uwalnianiu, po uzyskaniu satysfakcjonującej kontroli bólu i odpowiedniej dawki dobowej badanego leku (tramadol

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An abbreviated Ph.D. thesis

150-600 mg, morfina 20-200 mg), przez kolejne 28 dni chorym podawano tramadol (tabletki Tramal Retard) lub morfinę (tabletki MST Continus bądź kapsułki M-eslon) o kontrolowanym uwalnianiu. Ocenę JŻ przeprowadzano przy użyciu kwestionariusza EORTC QLQ C 30. Natężenie bólu oceniano wg skali VAS i słownej, natężenie objawów ubocznych wg skali słownej.

Wyniki. Czas leczenia Tramalem Retard wynosił 3-310 dni (średnio 87,15±78,23 dni), morfiną MST Continus i M-eslon 5-502 dni (średnio 100,05±102,67 dni). Zakres dobowych dawek stosowanych leków wynosił dla tramadolu 200-600 mg (średnia 322,22 mg ± 116,60), dla morfiny 20-270 mg (średnia 123,5 mg ± 78,15). W obu grupach chorych uzyskano korzystne efekty przeciwbólowe. W grupie chorych z bólem neuropatycznym natężenie bólu było mniejsze podczas leczenia morfiną (różnica statystycznie znamienna po 7 dniach leczenia). Większość leczonych chorych (80% w obu grupach) preferowała leczenie preparatami tramadolu i morfiny o kontrolowanym uwalnianiu. Leczenie było dobrze tolerowane, badanie ukończyło 17 chorych leczonych tramadolem i 18 otrzymujących morfinę. Objawy uboczne występowały częściej w grupie chorych leczonych morfiną, choć różnice znamienne obserwowano tylko w natężeniu senności, trudności w oddawaniu moczu, zawrotów głowy i pocenia. Badania JŻ wykazały lepszą ogólną JŻ i mniejsze natężenie zmęczenia po 35 dniach leczenia tramadolem.

Wnioski. Stosowanie drogą doustną tramadolu i ekwiwalentnych dawek morfiny (nie przekraczających 270 mg/dobę), o natychmiastowym i kontrolowanym uwalnianiu, stanowi skuteczny sposób analgezji u chorych z różnymi rodzajami bólu nowotworowego o umiarkowanym i silnym natężeniu. Tramadol jest mniej skuteczny w leczeniu bólu neuropatycznego. Oba leki mogą być bezpiecznie stosowane w warunkach domowych. Podawanie tramadolu związane jest z lepszą ogólną JŻ i mniejszym nasileniem zmęczenia po 35 dniach leczenia. Tramadol jest zalecany u chorych z bólem o umiarkowanym natężeniu (VAS 30-54 mm), a morfina u chorych z bólem o silnym i bardzo silnym natężeniu (VAS >54 mm). Ekwiwalentne dawki tramadolu i morfiny, podawane drogą doustną wynoszą 4:1.

Key words: analgesia, morphine, pain, tramadol
Słowa kluczowe: analgezja, ból, morfina, tramadol

The aim of the study was:
- to compare analgesic efficacy and side effects of tramadol and morphine, administered orally, in the treatment of different types of cancer pain in patients threated by home palliative care team,
- to assess analgesia, side effects and preference of the type of treatment expressed by patients receiving treatment with immediate release and controlled release preparations of tramadol and morphine,
- to establish the impact of type of the analgesic (tramadol or morphine) on patients' quality of life (QL),
- to establish equianalgesic oral doses of tramadol and morphine.

Patients and methods

An open, randomised prospective study was performed, with the participation of 40 patients staying at home, suffering from cancer pain of moderate, strong and very strong intensity, according to verbal scale and over 45 mm on VAS scale, demanding opioid analgesics administration. Patients were randomly assigned to one of the two groups:
- receiving tramadol.
- receiving morphine.

All patients gave their written consent for the participation in this trial. The Regional Ethics Committee at the Karol Marcinkowski Medical University approved conducting of the trial. The list of random assignment to one of the two groups was prepared by Statistical Department. Patients eligible for the study had to fulfil the following criteria:
- at least 18 years old,
- diagnosis of cancer,
- opioid – naive patients,
- oral route of tramadol or morphine administration,
- moderate, strong or very strong pain intensity according to verbal scale and at least 45 mm on the VAS scale that demanded opioid analgesic administration,
- overall state of the patients that allowed to expect completing the trial (total time of the study was 35 days),
- patients able to communicate effectively in order to fulfil EORTC QLQ C 30 questionnaire.

Patients with primary or metastatic brain tumours (pain caused by raised intracranial pressure) and patients with kidney insufficiency (creatinine level in serum >1.5 mg%) were excluded from the study. In statistical analyses significant differences were established on the level of $p<0.05$.

Using Mann-Whitney test no significant differences were found in the number of patients, gender, height, weight, age, activity (PS – performance status: ECOG and Karnofsky scale) between patients receiving tramadol and morphine.

In both groups of patients different diagnoses of primary tumours were found. Majority of patients in both tramadol and morphine group had primary tumours localised in alimentary system (7 and 4 patients), lung (5 in both groups), urinary system (3 and 4), other sites (5 and 7 patients respectively).

In both groups of patients different types of cancer pain occurred: visceral, bone, neuropathic and somatic from soft tissues. In the group treated with tramadol one type of pain appeared in 14 patients, two types of pain occurred in 6 patients; in the group treated with morphine in 15 and 5 patients respectively. Using Gauss test no significant differences were found in the frequency of visce-

ral, bone, neuropathic and somatic from soft tissues pain between patients' groups.

Pain was measured by VAS and 5-step verbal scale: 0 – no pain, 1 – weak, 2 – moderate, 3 – strong, 4 – very strong pain. Patients assessed analgesic effects of administered opioid according to 5 – step verbal scale: 1 – very good, 2 – good, 3 – moderate, 4 – weak, 5 – no effect.

Before starting the treatment patients treated with tramadol suffered from moderate (2 patients), strong (14 patients) and very strong (4 patients) pain intensity (verbal scale), according to VAS pain intensity was 47-99 mm (mean 82.05±16.01). Patients treated with morphine had similar pain intensity: according to verbal scale 1 patient had moderate pain, strong pain – 12 patients, very strong pain – 7 patients; using VAS scale pain intensity was 50--100 mm (mean 78.50±14.08). During first 7 days of the trial patients received tramadol or morphine in immediate release preparations (tramadol in drops or capsules, morphine in 0.5 % water solution). Both analgesics were administered every 4 hours, with a break during the night. The dose before sleep was increased by 50%. Starting doses were as follows: for tramadol 25-50 mg, for morphine 5 mg. Doses were adjusted depending on analgesia and side effects, usually increased by 50%.

During first 3 days of therapy in both groups of patients metoclopramide 10 mg t. i. d. was given as the prophylaxis of nausea and vomiting. After 3 days the treatment was stopped, but if nausea or vomiting appeared the therapy was continued or restarted.

After 7 days of the therapy with immediate release forms of opioids, if satisfactory pain control was achieved (VAS <50 mm or in verbal scale moderate, weak or no pain), patients were treated with controlled release formulations (in tramadol group – Tramal Retard (Long) 100, 150 and 200 mg tablets, in morphine group – MST Continus 10, 30, 60, 100 mg tablets or M – eslon 10, 30, 60, 100 mg capsules). To enter the second part of the study, patients had to receive daily doses of tramadol of 150-600 mg and morphine of 20-200 mg. Treatment with controlled release formulation lasted 28 days, total trial time was 35 days. During treatment with controlled release preparations, in case of breakthrough pain occur patients received tramadol and morphine in immediate release formulations. The rescue doses were 10-25% of the daily dose of the controlled release form of analgesic used regularly by the patient and usually were equal to the previous single immediate release doses of the drug during first 7 days of the treatment.

On the 7th day of the treatment with immediate release formulations of opioids (7th day of the trial) and also on the 14th and 28th day of the treatment with controlled release formulations of opioids (on 21st and 35th day of the trial respectively), patients filled EORTC QLQ C 30 questionnaire. At the same time, assessment of pain (verbal scale), analgesic effects of administered opioid (performed by patients), side effects of the treatment, performance status, heart rate, blood pressure, consumption of rescue analgesics used in case of breakthrough pain occurred were performed. Patients assessed pain intensity on the VAS scale once a week. On the 28th day of the treatment with controlled release opioids (35th day of the trial) patients assessed the therapy and their preference of type of the treatment (with immediate or controlled release formulation) which would be continued during follow up. Patients who preferred therapy with controlled release formulations of tramadol or morphine could continue this type of treatment for unlimited time.

Results

Among 20 patients treated with Tramal Retard (Long) the drug was administered through all period of the trial (28 days) in 17 (85%) patients. 3 patients (15%) discontinued treatment: 1 patient – after 3 days – because of side – effects, (she continued treatment with tramadol drops); 1 patient had unsatisfactory analgesic effect of Tramal Retard, (after 7 days of therapy she returned to the treatment with tramadol drops and died on 34th day of the trial), in the third patient, after 21 days of Tramal Long administration it was necessary to change the oral for subcutaneous route; due to dyspnoea and insufficient analgesia Tramal Retard was substituted by morphine, she died on 30th day of the study. All patients who completed the study continued treatment with Tramal Long during follow up.

Of 20 patients treated with controlled release morphine 11 received MST Continus tablets, 9 with M-eslon capsules. 18 (90%) patients completed the 28 days of the therapy, 2 patients discontinued the treatment: 1 patient died on 25th day of the therapy with M-eslon (32nd day of the trial), the second patient stopped M-eslon therapy (dose 80 mg/day) on the 5th day because of side effects which disappeared after continuation of the treatment with equivalent dose (75 mg/day) of morphine water solution. Similarly as in the tramadol group all other patients continued treatment with controlled release morphine preparations after completing entire study period during follow up. All patients' data was included in statistical analysis of the results (also patients who received immediate release preparations and who died during the study period).

The time of the treatment with Tramal Retard (Long) was 3-310 (mean 87.15±78.23) days, with morphine MST Continus and M-eslon 5-502 (mean 100.05±102.67) days. The daily doses of analgesics was 200-600 (mean 322.22±116.60) mg for tramadol and 20--270 (mean 123.5 mg±78.15) mg for morphine.

The mean rescue doses of the studied analgesics used in case of breakthrough pain during 28 days of the treatment with controlled release preparations were 528.125 mg±845.98 (range 0-2800 mg) for tramadol and 235.98 mg±285.65 (range 0-1680 mg) for morphine.

In both groups of patients before and during the treatment (after 1st, 3rd and 5th week of the treatment) no significant differences in circulatory system parameters such as heart rate, systolic and diastolic blood pressure and performance status (both ECOG and Karnofsky scale) were observed.

Tab. I. Pain intensity – VAS scale (mean ± SD)

Pain intensity	Tramadol treatment	Morphine treatment	Statistical significance
Before starting the treatment	82.05 ± 16.01	78.50 ± 14.08	NS
After 1 week of the treatment	39.00 ± 24.51	30.50 ± 21.35	NS
After 2 weeks of the treatment	40.10 ± 20.50	34.85 ± 25.16	NS
After 3 weeks of the treatment	38.40 ± 19.35	36.10 ± 24.53	NS
After 4 weeks of the treatment	35.70 ± 21.22	38.05 ± 20.20	NS
After 5 weeks of the treatment	36.83 ± 20.98	39.47 ± 22.49	NS

Analgesic effects

Beneficial, comparable results of analgesic effects have been achieved during the treatment with tramadol and morphine. Results in patients treated with tramadol and morphine before commencing the therapy, during administration of immediate (after 1st week of the therapy) and controlled release formulations (after 2nd, 3rd, 4th and 5th week of the treatment) were compared. Comparison of mean values and standard deviation (SD) of pain intensity (VAS scale) is shown in Table I.

Using Mann – Whitney test no significant differences were found in pain intensity (VAS scale), between patients treated with tramadol and morphine, before commencing and during the treatment with immediate release (after first week) and controlled release (after 2nd, 3rd, 4th and 5th week of the treatment). Using Friedman's test significant differences were found in pain intensity before starting and after 1st, 2nd, 3rd, 4th and 5th week of the treatment in both groups. Comparison of pain measurements performed after the 1st week didn't reveal differences.

In both groups of patients pain was assessed by verbal scale before and after the 1st, 3rd, 5th week of the treatment. Using Friedman's test significant differences were found between pain intensity before starting the treatment and in consecutive measurements after 1st, 3rd and 5th week of the therapy in both groups of patients. However using Mann – Whitney's test no significant differences were found between patients treated with tramadol and morphine before commencing and after 1st, 3rd and 5th week of the treatment.

Results of pain treatment in patients treated with tramadol and morphine in different types of pain: visceral, bone, neuropathic and somatic from soft tissues are shown in Table II. Using Mann – Whitney test no significant differences have been found between patients treated with tramadol and morphine, before starting and during therapy in patients with visceral and somatic pain from soft tissues. In patients with bone pain its intensity before

Tab. II. Results of tramadol and morphine treatment in different types of pain – VAS scale (mean ± SD)

Type of Pain	Time of the treatment	Tramadol treatment	Morphine treatment	Statistical significance
Visceral	0	80.64 ± 18.46	79.00 ± 13.25	NS
	1	34.45 ± 22.45	24.92 ± 19.38	NS
	2	34.00 ± 16.74	36.33 ± 21.17	NS
	3	32.54 ± 16.47	36.75 ± 22.59	NS
	4	33.36 ± 23.82	37.08 ± 19.51	NS
	5	30.10 ± 19.74	32.45 ± 22.66	NS
Bone	0	89.43 ± 12.50	72.20 ± 10.38	$p<0.05$
	1	40.86 ± 28.26	26.80 ± 27.03	NS
	2	47.14 ± 22.99	31.80 ± 24.86	NS
	3	36.00 ± 25.11	37.20 ± 20.30	NS
	4	32.00 ± 15.98	35.20 ± 16.72	NS
	5	38.50 ± 16.23	39.80 ± 18.30	NS
Neuro-	0	83.80 ± 14.27	78.00 ± 13.64	NS
Pathic	1	57.00 ± 13.82	19.25 ± 16.28	$p<0.05$
	2	60.00 ± 24.38	43.00 ± 15.83	NS
	3	57.40 ± 22.03	46.50 ± 15.85	NS
	4	49.40 ± 21.87	43.50 ± 15.37	NS
	5	55.60 ± 23.07	45.50 ± 20.60	NS
Somatic from	0	72.67 ± 22.28	78.00 ± 13.64	NS
soft tissues	1	40.33 ± 24.92	19.25 ± 16.28	NS
	2	42.00 ± 15.39	34.00 ± 15.85	NS
	3	37.33 ± 18.52	39.50 ± 31.01	NS
	4	41.67 ± 22.72	40.50 ± 15.37	NS
	5	36.00 ± 28.28	42.20 ± 30.60	NS

Time of the treatment: 0 – before starting the therapy, 1 – after 1 week of the treatment, 2 – after 2 weeks, 3 – after 3 weeks, 4 – after 4 weeks, 5 – after 5 weeks of the treatment

therapy was greater in the tramadol group (significant difference), during therapy no significant differences were found between both groups. In patients with neuropathic pain, after first week of therapy significant difference appeared in morphine group (less pain intensity), apart from that in this type of pain no significant differences before and during the treatment were found. In all types of pain significant decrease in pain intensity was noticed before and during treatment with tramadol and morphine.

Patients assessed analgesic efficacy of tramadol or morphine (verbal scale) three times (after 1, 3 and 5 weeks). Using Mann – Whitney's test no significant differences were observed between tramadol and morphine treatment with immediate (after 1st week of the treatment) and controlled release preparations (after 3rd and 5th week of the therapy).

Side effects

In Tramal Retard group 3 patients (15%) discontinued the treatment; 2 patients of this group died during the study. 1 patient after 3 days (on 10th day of the study) discontinued Tramal Retard (daily dose 500 mg), because of side effects: intense sweating, anxiety, palpitations; she returned to the treatment with tramadol drops at the same dose which was much better tolerated and she continued the treatment until death. The second patient stopped treatment with Tramal Retard on 7th day (14th day of the study) in the dose of 200 mg/day, because analgesia was worse; she also returned to tramadol drops at the same dose with better pain control. From the 33rd day of the study tramadol was administered subcutaneously due to general deterioration and inability to swallow the drug. She died on the 34th day of the trial. The third patient after 21 days of the treatment (on 28th day of the study) with Tramal Retard in dose 400 mg/day, suffered from general deterioration, dyspnoea, confusion and increase in pain intensity. Tramal Retard was discontinued and morphine 40 mg/day was started subcutaneously, effective pain control and relief of dyspnoea were achieved; agitation was eliminated by midazolam in the dose 20 mg/day. After 2 days (on the 30th day of the trial) the patient died.

In the group treated with morphine, 2 patients (10%) didn't complete the study. 1 patient received M--eslon (80 mg/day), after 5 days of the treatment (on the 12th day of the study) she discontinued therapy due to increasing side effects: malaise, shaking of legs, anxiety and worse analgesic effect. She returned to the treatment with morphine solution (75 mg/day) with better analgesia; side effects gradually disappeared. The second patient was treated with M-eslon (80 mg/day) until death (he died on the 25th day of the treatment, 33rd day of the trial) with good analgesic effect.

Side effects were the cause of discontinuation the therapy in 1 patient treated with Tramal Retard and in 1 patient treated with morphine M-eslon. In remaining patients side effects didn't cause cessation of treatment with Tramal Long or MST Continus and M-eslon. Respiratory depression, allergy or other serious adverse events connected with tramadol or morphine administration were not observed.

The most frequent side effects in both groups of patients were dry mouth, constipation and drowsiness, especially in morphine group. Laxatives were used in 12 (60%) patients treated with tramadol (3 patients received 2 laxatives, other received 1 laxative) and 14 (70%) patients treated with morphine (in this group 5 patients received 2, 3 or 4 laxatives).

The most rare side effects in both groups were mental disorders (confusion) and vomiting. All symptoms appeared more frequently in morphine group, however significant differences (using Mann – Whitney's test) were observed only in drowsiness (after 1st, 3rd and 5th week of the treatment), difficulties in passing urine and dizziness (after 3rd week of the treatment) and sweating (after 1st week of therapy).

Follow up

Before summing up results of the study 5 (25%) patients continued the treatment with Tramal Retard; 3 (15%) discontinued the treatment during the trial. From remaining 12 (60%) patients who completed the study 8 died. In this group 2 patients received tramadol until the end of life by subcutaneous route, in the remaining 6 patients due to increase in pain intensity while on Tramadol Retard (5 patients) and due to severe dyspnoea (1 patient) in spite of good analgesia it was necessary to substitute tramadol by morphine.

Until working out results of this study the treatment with controlled release morphine formulation was continued by 4 (20%) patients: 2 received M-eslon capsules, 2 MST Continus tablets. The remaining 14 (70%) patients died after completing the study; 2 (10%) discontinued the treatment with controlled release morphine during the trial.

From the group of 14 patients who died after completing the trial 3 (21%) patients received controlled release preparations of morphine until the end if life (MST Continus Tablets 2, M-eslon capsules 1), 1 (7%) patient discontinued treatment with MST Continus tablets because pain has disappeared (patient did not demand any analgesics), 10 (72%) patients received morphine subcutaneously: 6 because of inability to swallow for short period of time during agony, 3 due to nausea and vomiting, 1 patient demanded continuous, subcutaneous infusion of morphine with ketamine due to severe neuropathic pain.

Preference of the treatment

In tramadol group 16 (80%) patients assessed Tramal Retard treatment higher, 1 (5%) patient assessed treatment with drops and retard tablets as equally effective, 2 (10%) patients who discontinued the treatment with Tramal Long preferred tramadol in drops.

In morphine group 16 (80%) patients assessed MST Continus and M-eslon higher than morphine in water solution, 2 (10%) patients assessed both types of treatment

as equally effective, 1 (5%) patient who discontinued treatment with M-eslon preferred morphine in water solution, 1 (5%) patient didn't express preference.

Quality of life assessment

QL assessment was performed using EORTC QLQ C 30 questionnaire in both groups of patients on 7th, 21st and 35th day of the trial.

There were no differences in the results in the first QL measurement, both in functioning and symptoms scales between patients treated with tramadol and morphine. Similar results occurred in the second QL measurement apart from financial impact which was bigger in patients treated with morphine but the difference was only near significant (p=0.054).

In the third QL measurement significant difference appeared (p=0.001) in the emotional functioning, it was better in morphine group. In financial impact significant difference was noted (p=0.026), patients treated with morphine had more financial problems. No significant differences were observed in other functioning and all symptom scales.

Two factorial analysis of variance of functioning scales was performed. Functioning scales of EORTC QLQ C 30 were dependent variables, type of the treatment (tramadol or morphine) and time of QL measurement were independent variables. Main effects were patients' group (treated with tramadol or morphine), time of QL measurement and their interaction. In case significant difference occurred in main effects, finding in which measurements differences were significant was based on LSD (least difference) test.

In physical, cognitive and social functioning no significant differences were found in any of the explored main effects. In role functioning (work) differences were observed depending on period of the treatment. LSD test revealed significant differences between 1 and 3 measurement (tramadol group), between 1 and 3, 2 and 3 measurement (morphine group); between 1 (tramadol), 2 and 3 measurement (morphine) also between 2 (tramadol) and 3 measurement (morphine).

In emotional functioning significant difference were found in all 3 main effects: type of the treatment, time of the QL measurement and their interaction. In tramadol group significant differences were found between 1 and 3, between 2 and 3 QL measurement; also between 1 (tramadol) and 1, 3 measurement (morphine), between 2 (tramadol), and 1, 3 measurement (morphine), between 3 (tramadol) and 1, 2, 3 measurements (morphine).

In global QL significant difference was found in interaction between patients' groups and time of QL measurement. LSD test revealed significant difference between 3 measurement in patients treated with tramadol and morphine – global QL was higher in tramadol group (p=0.05 – Fig. 1).

Two factorial analysis of variance of symptom scales was performed. Symptom scales of EORTC QLQ C 30 were dependent variables, type of the treatment (tramadol or morphine) and time of QL measurement were independent variables.

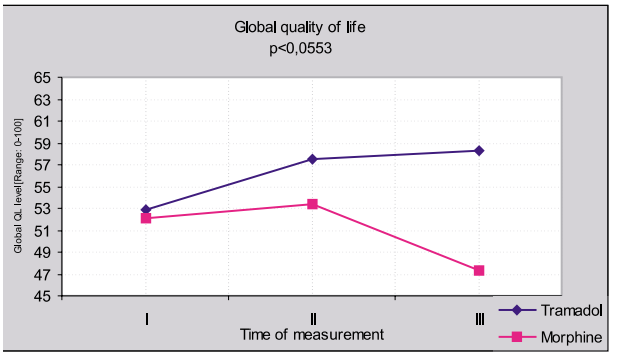

Fig. 1. Global QL: interaction of the type of the treatment and time of the QL measurement. Higher score means better QL

In most symptom scales (nausea and vomiting, pain) and single items (dyspnoea, sleep disturbance, constipation, diarrhoea) no significant differences were found. Using two factorial analysis of variance significant differences in fatigue and two items: appetite loss and financial impact were detected.

In fatigue and appetite loss scales an interaction between patients' groups and time of QL measurement was found. In fatigue scale significant difference was found between 1 and 3 measurement (tramadol), between 2 and 3 measurement (morphine), between 2 measurement (tramadol) and 3 (morphine), between 3 measurement (tramadol) and 1 and 3 (morphine). The intensity of fatigue was bigger in all three measurements in the morphine group (Fig. 2).

Significant differences were found in loss of appetite between 1 and 2 measurement (tramadol) and 2 measurement (morphine) and between 1 and 2, 2 and 3 measurement (morphine).

Significant differences were not observed in pain scale. Pain control was slightly better in the second and third QL assessment in tramadol group (not significant). In the first QL assessment results in both groups were nearly the same.

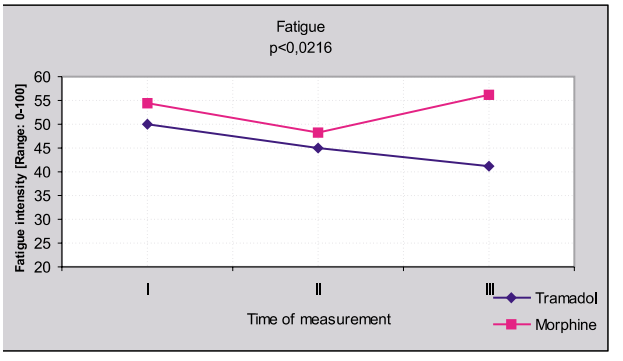

Fig. 2. Fatigue intensity: interaction of the type of the treatment and the time of the QL assessment. Higher score means bigger intensity of the symptom and worse QL
Explanations: Time of measurement: I – after first week of the treatment, II – after third week of the treatment, III – after fifth week of the treatment

Effect of the group was observed in financial problems. Patients treated with morphine had more problems. Significant differences were observed between all 3 measurements in tramadol and morphine group.

Discussion

Beneficial, comparable analgesia was achieved during treatment with tramadol and morphine expressed by the significant decrease of pain intensity after first week of therapy. The results indicate on high analgesic efficacy of tramadol (drops, capsules) and morphine (water solution) in immediate release formulations. Similarly during next four weeks of the treatment with controlled release tramadol (Tramal Retard 100, 150, 200 mg tablets) and morphine (MST Continus 10, 30, 60, 100 mg tablets and M-eslon 10, 30, 60, 100 mg capsules) good analgesic effect in both groups was maintained [1]. No difference in VAS, verbal scale and patients' assessment of analgesia was noted between both treated groups. These results indicate for good analgesic efficacy of controlled release formulations of tramadol and morphine.

There is an interesting trend in achieving better results with tramadol and slightly worse results with morphine (both in controlled release formulations) during the course of the trial. This trend however didn't achieve statistical significance in any time.

Beneficial, comparable analgesic effects were achieved in both groups in visceral pain (VAS <40 mm). In somatic pain from soft tissues after first week morphine was more effective than tramadol (mean VAS 19 and 40 mm respectively) but this difference wasn't significant. After 2nd, 3rd, 4th and 5th week results in both groups were similar. In bone pain its intensity at the beginning was stronger in the tramadol (VAS 90 mm) than in morphine (72 mm – significant difference) group and this could have contributed to slightly better results (not significant) after 1st (41 vs 27 mm) and 2nd (47 vs 32 mm) week in morphine group. In next measurements results in both groups were similar.

In neuropathic pain after 1st week results were significantly better in morphine than in tramadol group (mean VAS 19 and 57 mm respectively). This trend was maintained during all the trial period. Treatment with tramadol in this type of pain was less effective (mean VAS 49-60 mm). Morphine, especially in water solution was more effective. It is understandable regarding less sensitivity of this type of pain to opioid analgesic therapy. Usually high doses of strong opioids with adiuvant analgesics are required to achieve effective pain relief.

In significant number of patients (63.6%) treated with tramadol after completing the study period (mean time of therapy 48 days), it was necessary to substitute tramadol by morphine; in most patients (54.5%) the reason for change was inadequate pain control, in the rest (9.1%) the cause was severe dyspnoea. In the retrospective part of this study (not depicted in this paper) substitution for morphine was necessary in 35% (31% because of inadequate pain control) of patients treated with tramadol. The mean time of tramadol treatment was 52 days. In other studies the rates of change are different e. g. 70 % [2]; in our own studies 33% [3] and 35% [4]. In Grond's study [2] tramadol was safe and effective for mean time of 28 days – then it was changed for morphine. It seems that treatment with tramadol can be effective, however in 30-70 % of patients after different period of time (mean 28-52 days) it is necessary to change the drug for morphine or alternative strong opioid (e. g. transdermal fentanyl). This is connected with increase in pain intensity caused by cancer progression. In a small proportion of patients the reason for change is severe dyspnoea which can be ameliorated by morphine; this reason is more frequent in patients with primary or secondary lung or mediastinal tumours.

Majority of patients (80%) in both groups preferred treatment with controlled release formulations. It is in accordance with literature; this form of treatment is more convenient and improves compliance. Usually controlled release formulations of tramadol [5] and morphine [6] are administered every 12 hours; they are rarely taken every 8 hours. Immediate release formulations of morphine and tramadol usually are taken every 4 hours [7].

Very good toleration of the treatment was noted with immediate release formulations of tramadol and morphine – no one patient stopped the treatment because of side effects. Good toleration was noted during treatment with controlled release formulations of both drugs. However 3 patients in tramadol group discontinued therapy with Tramal Retard: one (500 mg/day) because of side effects (sweating, anxiety, palpitations) returned to tramadol in drops and side effects disappeared, one (200 mg/day) because of inadequate analgesia returned to the treatment with tramadol drops with better analgesia, and the last one (400 mg/day) because of agitation, dyspnoea and inadequate analgesia demanded morphine administered subcutaneously (40 mg/day); after this change improvement in pain control was noted.

In morphine group 2 patients discontinued the treatment with M-eslon: one patient died during the study – he received the dose 80 mg/day until death with satisfactory analgesia, the second patient was treated with the same dose of M-eslon – she experienced muscle tremor, anxiety and inadequate analgesia – after 5 days she returned to the treatment with morphine water solution (75 mg/day) with better analgesia and disappearance of side effects. These results indicate for slightly better toleration and slightly better analgesia (it concerns mainly morphine) with immediate release formulations. It is interesting that analgesia with Tramal Retard improved (not significantly) in comparison to drops or capsules. It is difficult to explain this effect; maybe the non – opioid mode of action is responsible or as suggested by some authors [8] lack of tolerance during tramadol treatment. During treatment with morphine the best scores were achieved with water solution; then analgesia was slightly worse (not significant). It can be caused either by development of tolerance for analgesia or by increase in pain intensity or by observed in some patients unwillingness to escalate the do-

se of morphine. These problems need clarification in controlled, clinical trials.

Side effects observed during the study were usually of mild or moderate intensity. In all explored side effects their intensity was bigger in morphine group; however in most cases they didn't reach statistical significance. Significant difference in constipation intensity in favour of tramadol (noted in retrospective study) was not observed in this prospective trial. It can be explained by more frequent gastrointestinal tumours in tramadol than in morphine group (35% vs 20%) and more frequent use of laxatives in the last group (70% vs 60%). 25% of patients on morphine received 2, 3 or 4 laxatives while only 15% on tramadol received 2 laxatives; the rest of patients in both groups were treated with just one laxative.

Drowsiness was more intense in morphine group (statistical significance in all 3 measurements); this is in accordance with other authors data [8, 9]. Significant differences were noted in difficulties in passing urine and dizziness (on 21st day of the study) and in sweating (on 7th day of the study) – all in favour of tramadol. The first two symptoms are sometimes observed in patients treated with morphine; however dizziness and sweating are typical side effects of tramadol. In patients treated with morphine these symptoms are connected with cerebellar ataxia, postural hypotension caused by alfa adrenergic receptors blockade (dizziness) and autonomic nerve system activation (sweating).

The increase of mean daily doses of tramadol was 17.24% and 11.03% after 3rd and 5th week of the treatment respectively (in comparison to the dose after first week of the treatment). This indicate that the biggest increase of dose is noted during first week of the treatment; the mean daily dose of tramadol after 5th week was even less than after 3rd week (322 mg and 340 mg respectively). These results seem indicating for good analgesia possibly connected with monoamine re – uptake blockade [10]. In our retrospective study [3] the increase of tramadol dose during 6 weeks of the therapy was 53% (from 260 mg after 1st week to 400 mg after 6th week) – this bigger increase could be connected with higher daily doses of tramadol (up to 900 mg) – in this study maximal dose was 600 mg/day.

The increase of mean daily doses of morphine was much bigger – 24.1% and 49.4% after 3rd and 5th week respectively (in comparison to the first week). Tawfik et al. [9] noted 7% increase of tramadol dose and 41% increase in morphine dose during 6 weeks of the treatment. Osipova et al. [8] concluded that tramadol dose was stable and MST Continus dose rose by 38.5% in this trial. Is the cause of morphine dose increments tumour progression or tolerance development for analgesia remains question to be answered. However, in this present study the daily doses of morphine during 5 weeks of the treatment did not exceed 270 mg and it confirms that most of cancer patients demand only small or moderate doses of morphine in order to achieve satisfactory pain control.

QL was assessed by QLQ C 30 questionnaire – QL assessment tool commonly used in cancer patients [11]. QL results in functioning scales showed stable level of physical functioning in both patients groups during the trial period. There was a trend of significant improvement in role functioning (work) observed between 2nd and 3rd QL measurement. The opposite tendency of significant decrease in cognitive, emotional and social functioning in both groups was noted also between 2nd and 3rd QL measurement. These results however were better in morphine group, especially in emotional functioning (statistical significance). Worse results in functioning scales could be caused by general deterioration observed in some patients. However this has no confirmation in ECOG and Karnofsky status changes; results of physical functioning (improvement) are also in conflict with these data.

In global QL there was a tendency towards better results in tramadol group since the 2nd measurement – it achieved statistical significance in the 3rd assessment. This can be explained by slightly better analgesia in tramadol group after 5 weeks of therapy and also by less intensity of drowsiness (all 3 side effects assessments) and fatigue (3rd QL measurement) in patients treated with tramadol.

QL data in symptoms scales showed no significant differences in nausea, vomiting and pain scale; also in single items: dyspnoea, sleep disturbances, constipation and diarrhoea. However intensity of all mentioned symptoms (with the exception of diarrhoea, nausea and vomiting) were greater in morphine group.

Two factorial analysis of variance revealed statistical difference in fatigue scale and loss of appetite scale. Fatigue intensity was greater in all 3 measurements in morphine group – in the third assessment it was statistically significant. Loss of appetite intensity was significantly lower in the 2nd measurement in morphine group.

In pain scale there was no significant difference between both groups. However pain scale in QLQ C 30 questionnaire is less accurate than VAS scale in the assessment of pain intensity [12].

In the financial impact effect of the group of treated patients was noted; more financial problems were in the morphine group; however this was caused by more difficult social situation and has no connection with drug price (morphine and tramadol in both immediate and controlled release formulations are free of charge for cancer patients in Poland). The difference between both groups was noted in all 3 measurements, but statistical significance was achieved only in the 3rd QL assessment.

There are no data comparing tramadol and small doses of morphine in terms of QL assessment. Brema et al. [13] compared in multicentre, randomised, long term study controlled release tramadol with buprenorphine using Spitzer Index QL; no difference between groups have been found, however patients and physicians assessed tramadol significantly higher.

In practice it is important to note that tramadol has little influence on gastrointestinal motility and causes less constipation in comparison to morphine. It can significantly improve QL and reduce cost of the treatment connected with the use of laxatives and enemas [14, 15]. Ano-

ther advantage of tramadol could be less cognitive impairment than morphine; it can be connected with less drowsiness and less fatigue observed in this study. However this issue is not definitely explored and cognitive impairment in patients with advanced cancer can be caused not only by opioid analgesics but also by many other factors like metabolic disturbances e. g. liver or renal impairment [16].

Equivalent analgesic doses of tramadol and morphine administered parenterally are about 10:1 [17]. Taking into account higher bioavailability of tramadol (over 70%) [18] than morphine (about 25-50%) [19] oral equivalent doses of these analgesics should be about 5:1. The comparison of mean daily doses of tramadol (297 mg) and morphine (68.5 mg) from retrospective study revealed the equivalent oral doses as 4.3:1. Similar results were achieved in another study [4], equivalent tramadol and morphine daily doses were 321 mg and 77.50 mg respectively indicating the ratio 4:1. Results in prospective study (mean daily doses of tramadol and morphine were 322 mg and 123.5 mg respectively) indicate the ratio 3:1. However taking into account that it was parallel study and over 63% of patients treated with tramadol demanded change for morphine it can be assumed that the ratio is about 4:1. It is in accordance with the only one controlled, cross – over study in cancer patients comparing tramadol and morphine [20] where the calculation of equivalent tramadol and morphine dose was 4:1.

There is no clear rule whether in patients with pain of moderate and severe intensity treatment should be started from weak or strong opioids [21]. It seems reasonable that in moderate pain intensity (VAS 30-54 mm) tramadol should be tried. In patients with severe pain (VAS >54 mm) oral morphine (EAPC recommendations) [22] or transdermal fentanyl are used but tramadol can be alternative for small doses of morphine in older and in patients with gastrointestinal disturbances. It is supported by results of Wilder – Smith et al. [20], Osipova et al. [8, 23], Rodrigues and Pereira [24] and own experience [4] also in this study. Further research is required focusing on pain control, side effects and particularly QL during long term treatment of cancer pain with tramadol in controlled clinical trials.

Introducing controlled release formulations of morphine [25,26] and tramadol [27] in Poland caused significant improvement in cancer pain treatment and patients' QL. Further progress is connected with the introduction of transdermal fentanyl in patches [28] and methadone [29] in solution which allowed for opioid rotation [30] if the treatment with morphine is unsuccessful.

Conclusions

1. The use of tramadol and equianalgesic doses of morphine not exceeding 270 mg daily, by the oral route, in immediate and controlled release preparations, allowed to achieve effective analgesia in patients with different types of cancer pain with moderate and strong intensity.
2. Tramadol is less effective in the treatment of neuropathic pain; strong opioids with appropriate adiuvant analgesics are recommended in this type of pain.
3. Immediate and controlled release preparations of tramadol and morphine administered orally can be safely used at home.
4. Most (80%) patients treated with tramadol and morphine preferred controlled release preparations.
5. Administration of tramadol is connected with better global QL and less fatigue after 5 weeks of the treatment.
6. Equianalgesic doses of morphine and tramadol administered orally are 1:4.
7. Tramadol should be administered in patients with moderate pain intensity (VAS 30-54 mm) and morphine is indicated in patients with strong and very strong pain intensity (VAS >54 mm).

Acknowledgements
I express my acknowledgements to my promoteur prof. Jacek Łuczak M. D., Ph. D. and also to Marek Powidzki M. A. and Elżbieta Nikisch Ph. D. from Statistical Department, Medical Academy in Poznań and to Mikołaj Majkowicz Ph. D. from the First Department of Psychiatry, Medical Academy in Gdańsk for assistance in statistical calculations.

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Paper received: 30 August 2000
Accepted: 21 January 2001