Efficacy and Safety of a Fixed Combination of Tramadol and Paracetamol (Acetaminophen) as Pain Therapy Within Palliative Medicine

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ABSTRACT

Goal: The goal of the research was to determine the efficacy of a fixed combination of tramadol and paracetamol (acetaminophen) in the treatment of pain of patients with the advanced stage of cancer.

Material and methods: A prospective study was conducted at the Center for Palliative Care, University Clinical Center Tuzla, Bosnia and Herzegovina, from January 1st to December 31st 2013. A total of 353 patients who were treated with a fixed combination of tramadol and acetaminophen (37.5 mg and 325 mg) at the initial dosage 3x1 tablet (112.5 mg tramadol and 975 mg acetaminophen) for pain intensity 4, up to 4x2 tablets (300 mg of tramadol and 2600 mg paracetamol) for pain intensity 7 and 8. If the patient during previous day has two or more pain episodes that required a “rescue dose” of tramadol, increased was the dose of fixed combination tramadol and acetaminophen to a maximum of 8 tablets daily (300 mg of tramadol and 2600 mg paracetamol). Statistical analysis was performed by biomedical software MedCalc for Windows version 9.4.2.0. The difference was considered significant for P<0.05.

Results: The average duration of treatment with a fixed combination tramadol and acetaminophen was 57 days (13-330 days). Already after 24 hours of treatment the average pain score was significantly lower (p<0.0001) compared to the admission day [5.00 (4:00 to 8:00) during the first days versus 2.00 (1:00 to 7:00) during the second day of treatment]. The average dose of the fixed combination tramadol and acetaminophen tablets was 4.8 ± 1.8 (180 mg of tramadol and 1560 mg paracetamol). Side effects, in the treatment of pain with a fixed combination tramadol and acetaminophen, were found in 29.18% of patients, with a predominance of nausea and vomiting.

Conclusion: Fixed combination of tramadol and acetaminophen can be used as an effective combination in the treatment of chronic cancer pain, with frequent dose evaluation and mild side effects.

Key words: carcinoma pain, fixed combination tramadol and paracetamol, side effects.

1. INTRODUCTION

Despite better knowledge of the neurobiology of pain, progress of pharmacology and techniques of pain treatment, consensus and guidance of experts, inadequate control and underestimation of pain more often is the rule rather than the exception (1). Approximately 30-40% of patients with cancer have pain at the time of setting the diagnosis. In the advanced stage of the disease 75-90% of patients suffer pain, despite data from the institution of palliative medicine around the world that 95% of cancer pain can be effectively controlled (2). In 40-50% of cases the pain was rated as medium-severe to severe, whereby in 70% of cases occurring in the form of nociceptive cancer pain wherein the cancerous cells released endothelin, prostaglandins and tumor necrosis factor alpha (TNF), proteolytic enzymes and other algogene substances. Compression and nerve injury or cancer pain due to infiltration of bone nerve are the cause of the neuropathic cancer pain (3).

Mild (weak) opioid analgesics are intended for the treatment of moderate pain and are used in case of treatment failure with non-opioid analgesics or if the initial pain intensity was 4 to 6 by the IAS, either alone or in combination with non-opioid, with or without other analgesics.

Tramadol is mild opioid analgesic with effects on the central nervous system, acting as a non-selective pure agonist of μ, δ and κ opioid receptors with higher affinity for the μ receptor. By inhibiting the reuptake of norepinephrine and serotonin release increase it was proved useful in neuropathic pain. Is used in the treatment of moderately severe pain, and can suppress the cough,
while in wide range of analgesic doses not suppress respiration. Depending on the method of application its efficiency amounts to 1/10 to 1/6 of morphine effectiveness.

There are evidences to support the central analgesic effect of paracetamol (4). To date has been proven the involvement of paracetamol in five different analgesic mechanisms: (a) Inhibition of isoenzymes of cyclooxygenase (COX) in the CNS without interaction with the binding sites; (b) Activation of serotonin bulboospinal time periods; (c) Activation of nitric oxide (NO) activation path; (d) Activation or modulation of endogenous opioid periods, and (e) Increase the tone of the endogenous cannabinoid (5). Metabolism of paracetamol releases N-acetyl-p-benzoquinone imine (NAPQI), which if it is not detoxified, binds to hepatocytes leading to cell necrosis. This binding is cause poisoning and liver weakness in case of paracetamol overdose (6). Also proven is link between hypertension and paracetamol (7, 8), which is probably caused by an significant amount of sodium which each paracetamol tablet contain.

Due to the frequent occurrence of mixed nociceptive-neuropathic pain, one analgesic may not be efficient enough to cover all of the causal mechanisms of pain. Combined analgesics may be more effective because they can offer a wider range of relieving pain, activation of analgesic process and reduce the negative effects (9). The effect of analgesics combination may be higher, lower or the same as the intended total extent of the impact. This effect can be calculated mathematically, based on the concept of ”equal dose”, which is defined as the dose of each drug that contributes to the total extent of the effect when each is used separately. Analysis can compare actual against expected effects of drug combinations (10).

The combined use of tramadol and paracetamol in one product, taking into account the pharmacokinetic and pharmacodynamic criteria can improve the benefit: risk ratio, increase efficiency by synergistic mechanisms, improve the tolerability of the drug (lower individual dose) and patient compliance (11).

Combining tramadol and paracetamol is achieved a synergistic analgesia by three different mechanisms of action: Binding of the μ-opioid receptors; Activation of the descending pain control pathways; Inhibition of COX-3. The combination ensures rapid onset of action, longer efficacy, better efficiency then individual components and a good safety profile. It can be administered alone or can be added to NSAIDs in patients with inadequate analgesia. Care must be taken that tramadol may increase the risk of convulsive spasms due to a decrease of convulsive threshold and lead to serotonin syndrome in combination with other selective serotonin reuptake inhibitors (antidepressants) (12). Paracetamol as the second component of the fixed combination in therapeutic doses has just few side effects, while the maximum recommended dose for adults (4 grams per day) is associated with cases of hepatotoxicity (13, 14).

Palliative stage of the disease involves interruption of targeted oncology treatments and the limited lifespan of the patient with the dominant aim of improving the quality of life, regardless of the duration of life (15). Pain of medium severe intensity is dominant symptom in patients with advanced stages of cancer. Progression of the disease in these patients requires frequent evaluation of symptoms of pain and adjustment of therapeutic doses of weak opioids or switch to strong opioid analgesics.

2. GOAL

The goal of the research was to determine the efficacy of a fixed combination tramadol and acetaminophen in the treatment of pain in patients with the advanced stage of cancer.

3. MATERIAL AND METHODS

A prospective study was conducted at the Center for Palliative Care, University Clinical Center Tuzla, Bosnia and Herzegovina, from January 1st to December 31st 2013. Study entered 369 patients who were due to pain intensity 4-8 (medium severe to severe pain) on the numeric rating scale (NRS), treated with a fixed combination of tramadol and acetaminophen (37.5 mg and 325 mg) in the initial dose 3x1 tablets for pain intensity 4, up to 4x2 tablets for pain intensity 7 and 8. Every day (10 days) pain intensity was recorded and if the previous day was patient had two or more episodes of pain, the dose of fixed combination tramadol and paracetamol was increased to a maximum of 8 tablets daily. During the first 10 days of study 16 patients were excluded (4.34%) (Table 1).

| The cause of exclusion from the study | Number of patients | The percentage of the total number of patients* |
|-------------------------------------|--------------------|-----------------------------------------------|
| Side effects (unsolved)             | 4                  | 1.08%                                         |
| Lethal outcome (during 10 days)     | 5                  | 1.37%                                         |
| Transfer to strong opiates          | 7                  | 1.89%                                         |

Table 1. Patients excluded from the study during the first ten days of treatment. * Of the total respondents, 369 patients

The study ended 353 patients, with mean age of 65.34±12.15 years (24-92 years), 211 (59.77%) males and 142 (40.23%) females. From the baseline 102 patients (28.89%) had verified the disease (lower individual dose) and patient compliance (11).

The combination of tramadol and paracetamol was increased to a maximum of 8 tablets daily. During the first 10 days of study 16 patients had two or more episodes of pain, the dose of fixed combination tramadol and paracetamol was increased to a maximum of 8 tablets daily. The study ended 353 patients, with mean age of 65.34±12.15 years (24-92 years), 211 (59.77%) males and 142 (40.23%) females. From the baseline 102 patients (28.89%) had verified the disease (lower individual dose) and patient compliance (11).

| Time from PH* diagnosis until palliative stage of the disease |
|-------------------------------------------------------------|
| Time from dg. to PSB* |
| < 3 mo. | 3 – 6 mo. | 7 – 12 mo. | 13 – 36 mo. | 37 – 72 mo. | > 73 mo. |
| No. of patients | 13 | 53 | 92 | 126 | 48 | 21 |
| Total (%) | 5.68 | 15.01 | 26.07 | 35.69 | 13.59 | 5.96 |

Table 3. Time from PH* diagnosis until PSB ** From total of 353 patients; **PH = histopathological diagnosis; PSB** = palliative stage of the disease
metastatic changes in bones while 251 patients (71.11%) had no bone metastases (p<0.0001).

In the study was 33.43% of patients with tumors of the gastrointestinal system, 25.22% with lung tumor, while the tumors of other organs account for less than 10%, with varying percentages of bone metastases (Table 2).

From total sample 158 (44.76%) patients were in the palliative stage of cancer disease in period less than 12 months, and 195 or 55.24% of the patients in the period after 12 months (p=0.067) (Table 3).

In 13 (3.68%) of patients palliative stage of the disease is verified in less than three months, with 126 (35.69%) in the period up to 36 months, while in 48 (13.59%) patients specific oncological treatment lasted up to 72 months and in 21 (5.96%) cases for more than six years.

The study was conducted in accordance with the Helsinki Declaration. All patients were previously informed about the aims and nature of research, and they provided their approval with written informed consent to participate in the study. Statistical analysis was performed by biomedical software MedCalc for Windows version 9.4.2.0. For testing the repeated measurements of dependent samples, depending on the distribution of variables were used paired t-test and Wilcoxon’s test. The statistical hypotheses were tested at the level of significance of α=0.05 or the difference between samples was considered significant if P<0.05.

4. RESULTS

a) The duration of treatment with a fixed combination tramadol and acetaminophen

The average duration of treatment with a fixed combination tramadol and paracetamol for all 353 patients was 57 days (from the shortest treatment duration of 13 to the longest of 330 days). Most common duration of treatment was between 31-100 days (in 225 patients or 63.74%), while 2 patients (0.57%) had treatment duration was longer than 300 days (Table 4).

The average pain score in all patients for 10 days of treatment was 2.12±1.34 where there was a statistically significant difference (p=0.0001) compared to the total intensity of pain in patients with metastatic changes in bones (2.26±1.47) compared to patients without bone metastasis (2.06±1.27). On the first day of treatment the average intensity of pain in all patients was 5.54±1.18, significantly more (p<0.0001) compared to the pain intensity on the tenth day of treatment 1.5±0.53 (Table 5).

The average pain score in all patients for 10 days of treatment was 2.12±1.34 where there was a statistically significant difference (p=0.0001) compared to the total intensity of pain in patients with metastatic changes in bones (2.26±1.47) compared to patients without bone metastasis (2.06±1.27). On the first day of treatment the average intensity of pain in all patients was 5.54±1.18, significantly more (p<0.0001) compared to the pain intensity on the tenth day of treatment 1.5±0.53 (Table 5).

**Table 5. Average pain intensity by days of treatment among all patients. $\frac{\$}{\text{measured outside of pain breakthrough}}$ Median, Wilcoxon test; $\frac{\text{“Paired samples t-test”}}{\text{(t-test)}}$.

| Day | Pain intensity | Day | Pain intensity | p |
|-----|--------------|-----|--------------|---|
| 1   | 5.00 (4.00 – 8.00) | 2   | 2.00 (1.00 – 7.00) | < 0.0001* |
| 3   | 2.00 (1.00 – 5.00) | 4   | 2.00 (1.00 – 6.00) | 0.097* |
| 5   | 2.00 (1.00 – 6.00) | 6   | 2.00 (1.00 – 5.00) | 0.036* |
| 7   | 2.00 (1.00 – 4.00) | 8   | 2.00 (1.00 – 5.00) | 0.26* |
| 9   | 2.00 (1.00 – 3.00) | 10  | 1.00 (1.00 – 3.00) | 0.003* |
| 1   | 5.54 ± 1.18 | 10  | 1.5 ± 0.53 | < 0.0001** |

Comparing the average values of pain intensity by days of treatment of patients with and without bone metastases, on the day of admission the pain intensity was significantly higher (p<0.0001) in patients with bone metastases [median 6.00 (4.00 to 8.00)] versus patients without bone metastases [median 5.00 (4.00 to 8.00)] (Table 6).

**Table 6 Comparison of average pain intensity of patients with and without bone metastases. Presented as Median; $\frac{\text{“Mann-Whitney test (independent samples)“}}{\text{“(independent samples)“}}$.

| Day | With bone metastases | Without bone metastases | p* |
|-----|----------------------|-------------------------|---|
| 1   | 6.00 (4.00 – 8.00) | 5.00 (4.00 – 8.00) | < 0.0001 |
| 2   | 2.00 (1.00 – 7.00) | 2.00 (1.00 – 4.00) | 0.12 |
| 3   | 2.00 (1.00 – 5.00) | 2.00 (1.00 – 4.00) | 0.07 |
| 4   | 2.00 (1.00 – 4.00) | 2.00 (1.00 – 6.00) | 0.64 |
| 5   | 2.00 (1.00 – 4.00) | 2.00 (1.00 – 6.00) | 0.004 |
| 6   | 2.00 (1.00 – 5.00) | 2.00 (1.00 – 3.00) | 0.044 |
| 7   | 2.00 (1.00 – 4.00) | 2.00 (1.00 – 3.00) | 0.54 |
| 8   | 2.00 (1.00 – 3.00) | 2.00 (1.00 – 5.00) | 0.004 |
| 9   | 2.00 (1.00 – 3.00) | 2.00 (1.00 – 3.00) | 0.54 |
| 10  | 2.00 (1.00 – 3.00) | 1.00 (1.00 – 3.00) | 0.13 |

**Table 4 Duration of treatment with a fixed combination tramadol and acetaminophen. $\frac{\text{“Total 353 patients“}}{\text{“(independent samples)“}}$.

| Days of treatment | No. of patients | %   | Transfer to morphine | Lethal outcome |
|-------------------|----------------|-----|----------------------|----------------|
| 1-30              | 59             | 16.71| 14                   | 12             |
| 31-60             | 128            | 36.26| 10                   | 17             |
| 61-100            | 97             | 27.48| 18                   | 9              |
| 101-150           | 41             | 11.61| 6                    | 5              |
| 151-200           | 11             | 3.12 | 3                    | 5              |
| 201-250           | 8              | 2.27 | 4                    | 3              |
| 251-300           | 7              | 1.98 | 4                    | 1              |
| > 301             | 2              | 0.57 |                      |                |

In patients with bone metastases, the average duration of treatment with a fixed combination tramadol and acetaminophen was 69 days (14-330), and in patients without bone metastases, the median duration of treatment was 52 days (13-278), which is significantly lower than compared to patients with bone metastases (p=0.0047).

In our study, disease progression and higher pain intensity was sign for transfer to strong opiates in 57 (16.15%) patients, while until the end of life the pain was adequately treated with a fixed combination tramadol and acetaminophen in 51 patients (14.45%) (Table 4).

b) Analysis of the pain intensity by days of treatment for all patients

Significantly greater pain intensity was also observed in patients with bone metastases on fifth, sixth and eighth days of treatment with a fixed combination of tramadol and paracetamol compared to patients without bone metastases (Figure 1).

Analysis of the optimal dose of fixed combination tramadol and paracetamol as the base of analgesics in the treatment of moderate pain

Figure 1. Mean pain intensity by days of treatment of patients with and without bone metastases
The average dose of the fixed combination tramadol and paracetamol (1 tablet = 37.5 mg and 325 mg) for all 353 patients for 10 days of treatment was 4.8±1.8 tablets (180 mg of tramadol and 1560 mg of paracetamol). The average dose of fixed combination tramadol and paracetamol (for both groups of patients) was higher with each subsequent day of treatment of 4.17±1.53 tablets (156.4 mg tramadol and 1355.3 mg paracetamol) on first to 5.62 ±1.95 tablets (210.8 mg tramadol and 1826.5 mg paracetamol) on the tenth day of treatment (Table 7).

In all patients with confirmed bone metastasis mean dose of fixed combination tramadol and acetaminophen was statistically significantly higher (p<0.0001) compared to patients without bone metastasis [5.42±1.83 (203.25 mg tramadol and 1761.5 mg paracetamol) in patients with metastases versus 4.59±1.79 (172.13 mg of tramadol and paracetamol 1491.8 mg) in patients without bone metastases] (Table 8).

On the tenth day of treatment in the group of patients without bone metastases average dose of tramadol in fixed combination tramadol and paracetamol was 200.25 mg of tramadol, while on the same day in a group of patients with bone metastases average dose of paracetamol was statistically significantly higher (p<0.0001) and amounted to 236.3 mg of tramadol (Figure 2).

Nausea that was present in 39.8% and vomiting with 34.9% were the dominant side effects in the treatment of pain with a fixed combination tramadol and acetaminophen, while the dizziness was observed in 8 (7.77%) and somnolence in 2 (1.94%) patients (Table 9).

5. DISCUSSION

A study published in 2011 on the efficacy and safety of a fixed combination tramadol and acetaminophen in the treatment of medium to severe pain (16) states a significant analgesic efficacy of this combination with a reduction in average pain intensity from an initial 6.1 to 3.1, with 64.8% of patients described significant pain relief. Data from the same study indicate that 90.5% of patients have a high degree of satisfaction with treatment and 78.7% of patients assessed the general situation as much better. Of the surveyed 2663 patients with an average age of 73.6±6.6 years, 119 (4.5%) reported at least one side effect in form of as known and foreseeable ones.

Similar results were also confirmed by our research, while in

| Day | Group with bone metastases | Group without bone metastases | p* |
|-----|----------------------------|-------------------------------|----|
| 1   | 4.5±1.39                  | 4.03±1.57                     | 0.0008 |
| 2   | 4.6±1.49                  | 3.91±1.4                      | <0.0001 |
| 3   | 4.9±1.83                  | 4.03±1.57                     | <0.0001 |
| 4   | 4.9±1.83                  | 4.14±1.64                     | =0.0001 |
| 5   | 5.2±1.76                  | 4.39±1.62                     | =0.0001 |
| 6   | 5.7±1.82                  | 4.76±1.4                      | <0.0001 |
| 7   | 5.9±1.72                  | 4.97±1.74                     | <0.0001 |
| 8   | 5.9±1.75                  | 5.12±1.8                      | =0.0002 |
| 9   | 6.1±1.74                  | 5.27±1.9                      | 0.0003 |
| 10  | 6.3±1.83                  | 5.34±1.93                     | <0.0001 |
| Σ   | 5.42±1.83                 | 4.59±1.79                     | <0.0001 |

Table 8. Comparison of mean dose of fixed combination tramadol and paracetamol by days of treatment in the groups with and without bone metastases. *Mann-Whitney test (independent samples)

Figure 2. The average dose of tramadol in a fixed combination tramadol and paracetamol by groups and days of treatment

In the group of patients without bone metastases, on the tenth day of treatment, the average dose of paracetamol in a
our research at the start of the study (the first day of treatment) average pain intensity in all patients was 5.54±1.18 which was significantly higher (p<0.0001) compared to the pain intensity on the tenth day of treatment 1.5±0.53. Already after 24 hours of treatment by a fixed dose of tramadol and acetaminophen, the average pain intensity of all patients was significantly lower p<0.0001 [5.00 (4.00 to 8.00) on the first day compared to the average pain intensity 2.00 (1.00 to 7.00) on the second day of treatment] which indicates the rapid onset of the drug action.

Review paper, published in 2008 (17), the efficiency of a fixed combination tramadol and acetaminophen in the treatment of mild to moderate pain included 15 studies. Nine studies (double-blind trials with a treatment duration of 1-10 days) includes a total of 2537 patients with chronic degenerative diseases (with the emergence of pain) after trauma or postoperatively, showed that the most common average dose of fixed combination tramadol and paracetamol (37.5 mg and 325 mg) was from 4.3–4.5 tablets. In six studies in which the duration of treatment was 4-13 weeks for the bone–muscle pain, it was followed 1890 patients, and the mean daily dose of fixed combination tramadol and acetaminophen (37.5 mg and 325 mg) was 3.5–4.2 tablets daily. In our study an average dose of fixed combination tramadol and paracetamol for all 353 patients during 10 days of treatment was 4.8 ± 1.8 tablets (180 mg of tramadol and paracetamol 1560 mg). The average dose of fixed combination tramadol and paracetamol was higher with each subsequent day of treatment with 4.17±1.53 tablets (156.4 mg of tramadol and 1355.3 mg of paracetamol) on the first to 5.6±1.95 tablets (210.8 mg of tramadol and paracetamol 1826.5) on the tenth day of treatment.

In a study by Ajay et al. (18) a total of 204 patients with moderate to severe pain of muscle–narrow origin was treated with a combination of phenetermine (50 mg) and diclofenac sodium (75 mg) (group A) and a fixed combination of tramadol and acetaminophen (37.5 mg and 325 mg) (group B). The intensity of pain with the use of a fixed combination tramadol and paracetamol after 5 days of treatment (measured by VAS scale) is reduced from an average of 74 on the first day to 36.72 on the fifth day of treatment. However a combination of phenetermine (50 mg) and diclofenac sodium (75 mg) showed better efficacy in the treatment of pain, wherein the average intensity of pain on the first day was 70.74 and 20.74 of the fifth, which is statistically better (P = 0.0001) compared to treatment than with fixed combination of tramadol and paracetamol. Similar results on the efficacy of a fixed combination tramadol and paracetamol in the treatment of pain in a group of patients with bone metastases (muscle–bone pain) shows our research. In our study, the average pain intensity in patients with bone metastases (muscle–bone pain) on the first day of treatment was 6.07±4±1.1831, on the fifth day significantly lower 1.941±0.6265 (p<0.001) and on the tenth day of treatment 1.588±0.5691 (p<0.001) which supports the analgesic efficacy of a fixed combination tramadol and paracetamol.

This claim is confirmed by a study carried out on 336 patients with chronic back pain (19) where the initial pain intensity was 68.8; immediately after the start of treatment was reduced to 47.4 and after 3 months of treatment at even 1.8. In this study followed side effects of which the most common were nausea (12.0%), dizziness (10.8%) and constipation (10.2%). The average daily dose of tramadol and paracetamol was 4.2 tablets (158 mg of tramadol and 1369 mg of paracetamol).

Our findings show that the side effects, during the treatment of pain with a fixed combination tramadol and paracetamol were registered in 103 patients or 29.18%, with the dominance of nausea and vomiting. Study by Jayne Edwards et al. (20) reported frequency of side effects in 35.88% of patients in the treatment of pain with a fixed combination of tramadol and acetaminophen, wherein the dominant was vomiting (27.35%) and nausea (25.88%), but much less common headache (5.88%), dizziness (3.82%) and somnolence (1.47%). In a study by Rawal et al. (21) vomiting occurred in 28.8%, nausea in 25.8%, dizziness in 15.9% and somnolence in 9.1% of patients with pain treated with fixed combination tramadol and paracetamol.

Limitations of the research
There are a small number of studies in which was compared the use of fixed-dose drug treatment of the moderate to severe cancer pain, and lot more research on the treatment of some forms of non-carcinoma pain, especially skeletal and muscle. This study did not presented, nor the frequency nor the ways of cropping breakthrough of pain in our patients. Duration of life and other disorders that accompany the advanced carcinoma limit the accuracy of research.

6. CONCLUSION
Fixed combination of tramadol and acetaminophen can be used as an effective combination in the treatment of chronic cancer pain, with frequent dose evaluation and mild side effects.

CONFLICT OF INTEREST: NONE DECLARED.

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EVERY ARTICLES HAVE an easy solution for mild-moderate pain. Minerva Med. 2008; 99(4): 369-390.