Effect of Tramadol/Acetaminophen Combination Tablets in the Treatment of Chronic Pain

Seung Hoon Baek, M.D., Chul Hong Kim, M.D., Kyung Hoon Kim, M.D., Sang Wook Shin, M.D., Hae Kyu Kim, M.D., and Seong Wan Bulk, M.D.

Department of Anesthesiology and Pain Medicine, College of Medicine, Pusan National University, Busan, Korea

= Abstract =

**Background:** The aim of this study was to evaluate the efficacy of a tramadol/acetaminophen combination tablet in chronic pain management.

**Methods:** Two hundred fifty five adult patients, suffering from chronic pain, were administered tramadol/acetaminophen combination tablets for at least 4 weeks. The analgesic effect from the start to the finish of the study was evaluated by a numeric rating scale (NRS, from 0 to 10). The pain relief score was also recorded (initial NRS-final NRS), which was allocated as follows: no change (0 or aggravation), moderate (1-2), notable (3-4) or significant pain relief (5 or more). The usefulness of the tramadol/acetaminophen combination tablet was rated according to the NRS, the pain relief score, the appearance of side effect and the patient’s response, and categorized as not useful, useful or very useful.

**Results:** The mean NRS score decreased from 6.1 to 3.5. The pain relief scores were no relief, moderate relief notable relief, significant relief and not assessed in 17, 108, 95, 23 and 3, respectively. Side effects developed in only 5.7% of the 246 patients.

**Conclusions:** It was concluded that tramadol/acetaminophen combination tablet therapy had an additive effect in the treatment of chronic pain management when combined with other analgesics. (*Korean J Pain* 2004; 17: 234-238)

**Key Words:** Pain, Tramadol/Acetaminophen combination tablet.

INTRODUCTION

Modern pharmacological pain management is based on non-opioid and opioid analgesics. Tramadole/acetaminophen combination tablet is a combination analgesic product containing a centrally acting synthetic analgesic (tramadol hydrochloride) and an agent that inhibits prostaglandin synthesis in the central nervous system and blocks pain impulses in the peripheral nervous system (acetaminophen). Tramadol is referred to as an atypical opioid because it had opioid and nonopioid mechanisms of action. Tramadol binds weakly as an agonist to the μ-opioid receptors in the central nervous system and also inhibits the reuptake of norepinephrine and serotonin. Tramadol is an effective analgesic agent in the treatment of moderate to moderately severe acute or chronic pain.1) Acetaminophen, known as paracetamol, is a nonsteroidal anti-inflammatory drug with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity. The exact mechanism of action is unknown. Acetaminophen is primarily centrally acting, has no effects on platelet aggregation, and is a reversible inhibitor of cyclooxygenase, an enzyme involved in prostaglandin (PG) synthesis. An analgesic effect may be produced by a direct action on the pain threshold. This effect is believed to be due to the inhibition of PG synthesis or the inhibition of the synthesis or actions of chemical mediators or other substances that sensitize the pain receptors to mechanical or chemical stimulation.2-4)

A previously used combination drug, oxycodone with acetaminophen, is effective in management of acute or chronic pain.5) Adding acetaminophen to weak opioids can increase the anal-
gesic potency of the opioid component. Tramadol/acetaminophen combination tablet is composed of 37.5 mg of tramadol hydrochloride and 325 mg of acetaminophen per tablet.

The aim of this study was to evaluate efficacy of tramadole/acetaminophen combination tablet in treatment of chronic pain management.

MATERIALS AND METHODS

This study was a multiclinic and outpatient/inpatient study. Two hundred and fifty-five patients were administered tramadol/acetaminophen combination tablet (Ultracet® Janssen Korea) for the treatment of chronic pain. Three patients could not be assessed on a numeric rating scale (NRS), because they stopped visiting our hospital after 4 weeks. Additional inclusion criteria were an NRS of more than 4 (9 patients were excluded) at the start of study, and an age between 21 and 96 years old. All patients were required to be able to read and comprehend written instructions and to complete the pain assessment forms. In most of patients the study was processed more than 4 weeks, without any change in the dosage of previously administered analgesics. Thirty three patients were administered tramadol/acetaminophen combination tablet as the first analgesics, and 213 patients added tramadol/acetaminophen combination tablet from other analgesics administered previously. The initial dose was determined by the initial NRS, the dosage of other drugs, the origin of pain, and the patients’ age. After 1 week of administration, the dosage was increased in the patients with ineffective pain relief by one tablet, and the dosage was maintained in the patients with effective pain relief.

The effect was evaluated by NRS from its first administration until the finish of the study in an outpatient clinic or hospital room. In order to determine the effect of pain relief, the NRS score change was calculated (the initial NRS score-final NRS score) and grouped into 4 categories. Pain relief was evaluated as follows: aggravation or no change was no relief, a score change of 1 or 2 was moderate, a score change 3 or 4 was notable, and a score change of more than 5 was significant pain relief. Also, a physician evaluated the effect as not useful, useful, or very useful. Side effects were recorded at each visit. In cases of those who getting severe, the dosage of tramadol/acetaminophen combination tablet was reduced. The result of the effect of drug was examined using a paired t-test. A P value (0.01) was considered statistically significant.

RESULTS

The mean age was 46.1 years; 46 patients suffered from cancer pain, 64 patients from musculoskeletal pain, 29 patients from neuropathy, 87 patients from osteoarthritis (OA) or rheumatic arthritis (RA), and 20 patients from other pain. There were 161 female patients, and 94 male patients. The mean initial tramadol/acetaminophen combination tablet dosage was 2.5 tablet, and the final dosage was 2.9 tablet. Among the patients, 33 took tramadol/acetaminophen combination tablet as the initial analgesic, whereas the remaining patients were

| Table 1. Patient Number, Age, Sex, NRS, Dose of Tramadol/ Acetaminophen Combination Tablet and Development of Side Effects |
|------------------|-----|----------|--------|--------|------|
|                 | Age (yr) | Sex (M/F) | NRS ratio | Dose ratio | SE   |
| A               | 46    | 42.2     | 22/24   | 5.2/2.3 | 3.2/3.7 | 8    |
| B               | 64    | 49.5     | 38/26   | 6.4/3.8 | 3.1/3.2 | 3    |
| C               | 29    | 48.0     | 19/10   | 7.2/4.6 | 2.9/3.1 | 0    |
| D               | 87    | 43.5     | 17/70   | 6.1/3.8 | 2.1/2.2 | 2    |
| M               | 20    | 51.9     | 9/11    | 6.2/1.2 | 2.5/2.5 | 1    |
| Total           | 246   | 44.6     | 105/141 | 6.1/3.5 | 2.5/2.9 | 14   |

Data are number of patients. Numeric rating scale (NRS) ratio: initial NRS/final NRS, Dose ratio: initial dose/final dose (tablet), SE: side effects. A: cancer pain, B: musculoskeletal pain, C: neuropathy, D: osteoarthritis or rheumatic arthritis, M: others.

Fig. 1. Comparison of numeric rating scale (NRS) before and after tramadol/acetaminophen combination tablet treatment. Data are mean ± S.D. A: cancer pain, B: musculoskeletal pain, C: neuropathy, D: osteoarthritis or rheumatic arthritis, M: Others. *P < 0.01: initial NRS vs. final NRS.
medicated concurrently with other analgesics. The study period of the tramadol/acetaminophen combination tablet effect was 4 weeks in 75 patients, 8 weeks in 99 patients, 12 weeks in 55 patients and more than 4 weeks in 17 patients (Table 1).

In all patients, the mean NRS score decreased from 6.1 to 3.5. In the cancer pain group, the mean NRS score decreased from 5.2 to 2.3, in the musculoskeletal group from 6.4 to 3.77, in the neuropathy group from 7.2 to 4.6, in the OA/RA group from 6.0 to 3.8 and in the other pain group from 6.2 to 1.2 (Fig. 1).

In the evaluation of the efficacy of the tramadol/acetaminophen combination tablet for all patients, no relief (n=17), moderate relief (n=108), notable relief (n=95), significant relief (n=23), and 3 were not assessed (Fig. 2). According to the categories no relief, moderate relief, notable relief, significant relief, and not assessed, the number of patients in cancer pain group were 2, 15, 24, 5 and 0; the musculoskeletal group were 4, 23, 32, 4 and 1; the neuropathy group were 3, 10, 14, 2 and 0; the OA/RA group were 7, 50, 22, 6 and 2, and the other pain group were 1, 10, 3, 6 and 0 (Fig. 3).

The doctor’s evaluation depended on the NRS score change, the pain relief score, the development of side effects, the patient’s response, and the patient’s age divided by not useful

Fig. 2. Efficacy of tramadol/acetaminophen combination tablet for all patients. Percent values are representing the number of patients of the corresponding category to the total patients. No relief: numeric rating scale (NRS) aggravation or no change, Moderate relief: NRS decrease 1-2, Notable relief: NRS decrease 3-4, Significant relief: NRS decrease 5 or more.

Fig. 3. Comparison of Pain relief after tramadol/acetaminophen combination tablet treatment. A: cancer pain, B: musculoskeletal pain, C: neuropathy, D: osteoarthritis or rheumatic arthritis.

Fig. 4. Doctors assessment for the usefulness of tramadol/acetaminophen combination tablet in the management of chronic pain.

Fig. 5. Comparison of pain relief after tramadol/acetaminophen combination tablet treatment. A: cancer pain, B: musculoskeletal pain, C: neuropathy, D: osteoarthritis or rheumatic arthritis.
(n=29), useful (n=188), and very useful (n=20). Nine (9) patients are not assessed (Fig. 4, 5).

Side effects developed in only 14 patients during this study, but adverse effects were not severe and were soon remedied. These were nausea, somnolence, dizziness and constipation (Table 1).

DISCUSSION

The purpose of combination analgesics is to improve the effect of simple analgesics and to reduce side effects or toxicity. Tramadol/acetaminophen combination tablet is a combination analgesic having different action mechanisms, so it has a synergic effect. Its benefits are the complementary actions of the constituent analgesics: the rapid effect of acetaminophen and the sustained effect of tramadol. Tramadol/acetaminophen combination tablet is not a nonsteroidal anti-inflammatory drug (NSAID); it is not associated with gastrointestinal bleeding and ulcers. In clinical trials, constipation, somnolence, and increased sweating were the most frequent adverse effects associated with Ultracet; these were not significant and were soon remedied.

The efficacy of the Tramadol/acetaminophen combination tablet in all patients' groups was a significant decrease in NRS from 6.1 to 3.5. We analyzed followed by four groups (P < 0.01). In the cancer group, the NRS decreased from 5.2 to 2.3 and 63% of patients' pain relief evaluations were notable or significant pain relief. The WHO has recognized combination analgesics' benefits in cancer pain management. Tramadol/acetaminophen combination tablet does not contain any scheduled opioid, and it does not entail any serious abuse or dependence risk. In the musculoskeletal pain group the NRS decreased from 6.4 to 3.8, and 52% of patients' pain relief evaluation were notable or significant pain relief. Acetaminophen is used as a first-line analgesic for lower back pain. Also, tramadol is effective in musculoskeletal pain. A recent study has demonstrated the effect of tramadol/acetaminophen combination tablet on musculoskeletal pain. In the neuropathy group, the NRS decreased from 6.1 to 3.8, and 55% of patients' pain relief evaluations were notable or significant pain relief. Another recent study has demonstrated that tramadol is effective in diabetic neuropathy. In the OA/RA pain group, the NRS decreased from 6.1 to 3.8, and 32% of patients' pain relief evaluations were notable or significant pain relief. Acetaminophen is a first-line therapy in OA/RA patients because of its rapid action time, safety, and lower incidence of side effects. Also, tramadol is an effective and safe drug for long term use in arthritis pain.

A recent study has demonstrated the effect of tramadol/acetaminophen combination tablet in the treatment of acute or chronic pain. They evaluated only tramadol/acetaminophen combination tablet, so they had a wash out period more than 3 weeks, but in our study we used other drug in combination. During this study, coexisting drug dosage did not change, but maintained throughout the study period. Therefore, we concluded that tramadol/acetaminophen combination tablet is an effective adjuvant analgesic chronic pain management. Most of all case used other analgesics before tramadol/acetaminophen combination tablet had taken, but pain was not controlled. After 4 weeks or a longer period during which Ultracet was administered, significantly decreased NRS scores and pain relief. Before our study began, many patients had experienced adverse effects due to the high dosage of other analgesics, but after our study, most patients did not experience adverse effects. Tramadol/acetaminophen combination tablet, a low dosage of each medication can be administered, side effects are minimized, and a better result is achieved by this synergic mechanism.

We concluded that tramadol/acetaminophen combination tablet is an effective analgesic in acute or chronic pain management, which makes it a first-line or adjuvant analgesic.

REFERENCES