Efficacy and safety of tramadol/acetaminophen in the treatment of breakthrough pain in cancer patients

Ming-Lin Ho, MD, Chih-Yuan Chung, MD, Chuan-Cheng Wang, MD, Hsuan-Yu Lin, MD, Nicholas C. Hsu, BS, Cheng-Shyong Chang, MD.

ABSTRACT

الأهداف: تقييم مدى فعالية وسلامة الجمع بين أقراص الترامادول بمعدل 37.5 مليغرام (tramadol) والأسيتامينوفين بمعدل 325 مليغرام (acetaminophen) وذلك لعلاج درجات الألم المختلفة التي يعاني منها مرضى السرطان خلال اليوم.

الطريقة: لقد قمنا بإجراء دراسة مفتوحة التسمية (open-label study) في مستشفى شانغوا، تايوان وذلك خلال الفترة من يناير 2006م إلى فبراير 2007م. شملت هذه الدراسة 59 مريضاً مصاباً بالسرطان ويتعاطون الأفيون (opioid) لتسكين الألم، وكان هؤلاء المرضى يشكون من نوبات الألم التي كانت متوسطة على أقل تقدير وذلك وفقاً للسلم التماثلي البصري (Visual Analog Scale)، حيث قام معظم المرضى بتسجيل درجات الألم لديهم والتي وصلت إلى 40 مليمتر أو أكثر من أصل 100 مليمتر على السلم. وتم تحديد فعالية الجمع بين أقراص الترامادول و الأسيتامينوفين من خلال تسجيل درجات الألم على السلم التماثلي البصري وكذلك قياس الآثار الجانبية بعد مرور 10، و30، و60 دقيقة من أخذ هذه الأقراص، وبعد ذلك تم تسجيل النتائج على السلم التماثلي البصري بعد زوال الألم من المرضى.

النتائج: لقد كان متوسط درجات الألم التي سجلها المرضى على السلم التماثلي البصري قبل بدء العلاج وعند الشعور بالألم 77.8، وقد أظهرت نتائج التحليل تحسناً ملحوظاً في درجات الألم التي تنقسم خلال اليوم إلى 3 مرات وذلك بعد مرور 10، و30، و60 دقيقة من أخذ أقراص الترامادول والأسيتامينوفين ($p \leq 0.001$). لقد كان متوسط الوقت الذي استغرقته الأقراص لإزالة الألم 597.2 ثانية حيث كانت درجة الألم التي شعر بها المرضى حينها 43.4 وذلك وفقاً للسلم التماثلي البصري. وأظهرت النتائج أن تناول أقراص الترامادول والأسيتامينوفين معاً قد قام بتقليل درجات الألم على السلم بنسبة تصل إلى أكثر من 30%، حيث نقصت نسبة الألم بعد 10 دقائق بنسبة 74.6%، وبعد 30 دقيقة بنسبة 86.4%، وبعد ساعة بنسبة 94.9% ($p \leq 0.001$)، وقد أُصيبت حالتين بالنعاس من أثر العلاج.

خاتمة: أشارت الدراسة إلى احتمال فعالية وسلامة الجمع بين أقراص الترامادول والأسيتامينوفين في علاج درجات الألم المختلفة التي يعاني منها مرضى السرطان خلال اليوم.

Objectives: We evaluated the analgesic efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg combination tablet, for the treatment of breakthrough pain in cancer patients.

Methods: This study was conducted at Changhua Christian Hospital, Changhua, Taiwan from January 2006 to February 2007. The single-center and open-label study enrolled 59 opioid-treated cancer patients with at least moderate breakthrough pain (visual analog scale [VAS] score ≥40mm on a 100-mm scale). The efficacy measures included VAS scores and adverse effect assessment 10, 30, and 60 minutes after the administration of tramadol/acetaminophen. Visual analog scale score at time of pain relief was reported.

Results: The mean VAS score when the breakthrough pain episode began (0 minute) was 77.8. Analysis showed significant better mean pain VAS scores at 10, 30, and 60 minutes after the administration of tramadol/acetaminophen ($p \leq 0.001$ versus 0 min for all 3 time points). The mean time to pain relief was 597.2 seconds and the mean VAS score at time of relief was 43.4. The effective rates, defined by more than 30% reduction of the VAS score, after 10 minutes of administration was 74.6%, 30 minutes 86.4%, and one hour 94.9% ($p \leq 0.001$ versus 0 minute for all 3 time points). Two cases of drowsiness were reported.

Conclusions: Tramadol/acetaminophen might be efficacious and safe in the treatment of breakthrough pain in cancer.

Saudi Med J 2010; Vol. 31 (12): 1315-1319

From the Division of Chest (Ho), Department of Internal Medicine, Changhua Christian Hospital, Division of Hematology-Oncology (Chung, Wang, Lin, Chang), Department of Internal Medicine, Changhua Christian Hospital, Changhua, and the Graduate Institute of Medicine (Hsu), College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

Received 4th September 2010. Accepted 18th October 2010.

Address correspondence and reprint request to: Dr. Cheng-Shyong Chang, Division of Hematology-Oncology, Department of Internal Medicine, Changhua Christian Hospital, 135 Nanhsiao Street, Changhua County 500, Taiwan. Tel. +886 (4) 7238595 Ext. 1940. Fax. +886 (4) 7200931. E-mail: 15120@cch.org.tw

Many cancer patients experience episodic breakthrough pain during their illness. In cancer, breakthrough pain is an incidence of pain superimposed on an otherwise stable persistent pain in patients treated with opioids.[1] Breakthrough pain has a rapid onset and is usually unpredictable and heterogeneous. Oral dose forms of opioid take approximately 30 minutes to relieve pain,[2] and since pain relief is usually required urgently, are not adequate for the breakthrough pain. Intravenous rescue opioids have fast onset of action and are effective for the episodic pain. However, as in many countries, all opioids are controlled substances in Taiwan. Intravenous opioids are particularly tightly regulated analgesics, which are difficult for cancer patients and their doctors to get access to in a timely manner. Tramadol HCI is a centrally acting analgesic that combines micro (μ)-opioid receptor binding activity with the inhibition of serotonin/norepinephrine reuptake.[3] Acetaminophen is a clinically proven analgesic and antipyretic. It acts centrally via mechanisms that appear to comprise a synergistic interaction between spinal and supraspinal sites.[4] Acetaminophen has been demonstrated to enhance the therapeutic efficacy of tramadol.[5] The combination of tramadol HCI/acetaminophen provides a more rapid onset of action compared to tramadol HCI alone and a longer duration of action than acetaminophen alone,[6,7] and allow lower cumulative daily dosages of each drug to be used. The tramadol/acetaminophen combination tablet has been shown to be effective and well tolerated for the treatment of acute pain.[7,8] The purpose of this study was to examine the analgesic efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg combination tablet, in the treatment of breakthrough pain in cancer patients.

Methods. This study was conducted at Changhua Christian Hospital, Changhua, Taiwan from January 2006 to February 2007. The single-center and open-label study enrolled 39 opioid-treated cancer patients with at least moderate breakthrough pain. Inclusion criteria were as follows: patients must had been on a stable daily dose of weak opioids (codeine, tramadol) or strong opioids (morphine, fentanyl) for at least 72 hours prior to the start of the study and must remained at the same dosage for the duration of the study. Moderate breakthrough pain is defined as ≥40 mm on a 100-mm pain visual analog scale (VAS). A baseline pain intensity measurement in VAS prior to the start of the study was obtained from each inpatient. Written informed consents according to the guidelines of the Changhua Christian Hospital Institution Review Board were obtained from all enrolled patients. Exclusion criteria included history of allergy or hypersensitivity to tramadol or acetaminophen, use of either morphine with daily dose of more than 120 mg or fentanyl with daily dose of more than 50 μg/hour, and history of abuse of opioid analgesics prior to their diagnosis of cancer. Patients were not allowed to take antidepressants or anti-epileptic drugs, sedative hypnotics, selective serotonin reuptake inhibitor, short-acting analgesics (including acetaminophen), topical medications and anesthetics and/or muscle relaxants during the study. Pregnant and lactating females were also excluded. Both outpatients and inpatients with whom they meet the inclusion/exclusion criteria were recruited.

Intervention. Breakthrough pain is usually controlled with extra doses, calculated as 1/6 of the total 24 hour opioid dose, of the around-the-clock drug.[9] Tramadol 37.5 mg/acetaminophen 325 mg was administered according to the total daily dose of around -the-clock medications of each patient and the relative potency of the opioids (**Table 1**). Due to the toxicity of acetaminophen, no more than 2 tablets were given to patients in this study. The VAS was measured when a breakthrough pain episode began. Pain intensity scores and adverse effects were recorded at 10, 30, and 60 minutes thereafter. Pain relief was defined as a decrease of at least 30% in VAS. Time to pain relief was determined by the single stopwatch technique. The VAS score at the time when the breakthrough pain was relieved was reported. All VAS scores were taken by patients and recorded by a study nurse. Adverse effects were also reported by patients and evaluated by the physician investigator.

Statistical analysis. All statistical tests were interpreted at the 5% significance level (2-tailed). Patient's characteristics were presented as means (±standard deviation) for continuous variables and as proportions for qualitative variables. The degree of pain control was analyzed using paired t-test.

Table 1 - Study medication dosage for cancer patients.

Around-the-clock medication	Dosage	Breakthrough pain medication
Opioids	Oral daily dose	Tramadol /acetaminophen
Tramadol	≤300 mg	1 tablet
Codeine	≤400 mg	1 tablet
Morphine	<60 mg	1 tablet
Morphine	60-120 mg	2 tablets
Fentanyl	25-50 μg/hour	2 tablets

Disclosure. This study was supported by Johnson & Johnson, Taiwan Ltd, Taipei, Taiwan.

Results. Fifty-nine patients were enrolled in this study, 33 patients were male and 26 patients were female. Forty-seven patients had cancer that has metastasized while 12 patients did not. The mean age was 60.96 years. Regarding cancer origin, lung cancer was ranked as the most prevalent (61%), followed by cancer of the intestines (15.3%), and head and neck (11.9%). The most frequently used around-the-clock analgesic medication in studied patients was tramadol 50 mg (31 patients), followed by fentanyl 25 mg/hour (12 patients), and morphine 10 mg (10 patients). The demographic and baseline characteristics of the patients are summarized in **Table 2**. We collected baseline VAS scores from 39 inpatients (mean = 17.4). Baseline VAS readings of the 20 outpatients enrolled were not recorded because the breakthrough pain episode had already begun at the time of their outpatient visit. The mean VAS score when the breakthrough pain episode began (0 min) was 77.8. The numbers dropped drastically to 38.5 at 10 minutes, 24.2 at 30 minutes, and 16.3 at one hour after the administration of tramadol/acetaminophen ($p \leq 0.001$ versus 0 min for all 3 time points). Statistically significant improvements in pain scores were observed immediately after the administration of tramadol 37.5 mg/acetaminophen 325 mg. The mean time to pain relief was 597.2 seconds and the mean VAS score at time of relief was 43.4 for all patients (**Table 3**). The effective rates of tramadol/acetaminophen, defined by more than 30% reduction of the VAS score, after 10 minutes of administration was 74.6%, 30 minutes 86.4%, and one hour 94.9% ($p \leq 0.001$ versus 0 min for all 3 time points) (**Table 4**). Two of the fifty-nine enrolled patients took 2 tablets in this study; the rest only had one. Only 2 cases of mild drowsiness were reported.

Discussion. Breakthrough pain is highly prevalent in the cancer population and affects the quality of life in profoundly negative ways.[10] It has been increasingly recognized in recent years. Identification of a drug,

Table 2 - Demographics of the studied cancer population (N=59).

Characteristics	n	(%)
Age, years		
Mean±SD	60.96 ± 14.8	
Medium (range)	62.21	(23.99 - 90.03)
Gender		
Female	26	(44.1)
Male	33	(55.9)
Metastasis		
No	12	(20.3)
Yes	47	(79.7)
Organ		
Lung	36	(61.0)
Intestine	9	(15.3)
Head & Neck	7	(11.9)
Stomach	2	(3.4)
Hematopoietic	2	(3.4)
Breast	1	(1.7)
Genitourinary	1	(1.7)
Reproductive System	1	(1.7)
Around-the-clock medication		
Fentanyl 25 ug/hr	12	(20.3)
Fentanyl 50 ug/hr	3	(5.1)
Morphine 10 mg	10	(16.7)
Codeine 30 mg	2	(3.4)
Tramadol 50 mg	31	(52.5)
Tramadol 50 mg + Fentanyl 25 µg/hr	1	(1.7)

Table 3 - Efficacy result of VAS in studied cancer population.

Characteristics	Results	*P*-value versus 0 minute
VAS baseline		-
Mean (SD)	17.4[a] ± 24.7)	
Median	10.0	
Range	0.0 - 90.0	
VAS 0 min after tramadol/acetaminophen		-
Mean (SD)	77.8 ± 18.9	
Median	80.0	
Range	40.0 - 100.0	
VAS 10 min after tramadol/acetaminophen		≤0.0001
Mean (SD)	38.5 ± 25.2	
Median	40.0	
Range	0.0 - 90.0	
VAS 30 min after tramadol/acetaminophen		≤0.0001
Mean (SD)	24.2 ± 22.8	
Median	20.0	
Range	0.0 - 70.0	
VAS 60 min after tramadol/acetaminophen		≤0.0001
Mean (SD)	16.3 ± 19.0	
Median	10.0	
Range	0.0 - 60.0	
Time to pain relief in second		-
Mean (SD)	597.2 ± 373.4	
Median	493.0	
Range	128 - 1543	
Vas at time of pain relief		-
Mean±SD	43.4 ± 22.4	
Median	50.0	
Range	0.0 - 90.0	

[a]N=39. VAS - visual analog scale, SD - standard deviation

Table 4 - Effective rate of tramadol/acetaminophen (N=59).

Characteristics	n (%)	*P*-value versus 0 minute
10 min after tramadol/acetaminophen		≤0.0001
VAS reduction >30%	44 (74.6)	
VAS reduction ≤30%	15 (25.4)	
30 min after tramadol/acetaminophen		≤0.0001
VAS reduction >30%	51 (86.4)	
VAS reduction ≤30%	8 (13.6)	
60 min after tramadol/acetaminophen		≤0.0001
VAS reduction >30%	56 (94.9)	
VAS reduction ≤30%	3 (5.1)	

VAS - visual analog scale

which has a time course that matches the experience of the pain, would provide a great relief for patients. Breakthrough pain is typically of rapid onset; therefore, analgesic drugs with a rapid onset of effect would be more effective in pain management. The current approach to managing breakthrough pain with rescue medication often involves giving an additional dose based on the patient's around-the-clock analgesia and the potency ratio with oral morphine of the opioids.[9,11-16] Breakthrough pain relief is usually required urgently and most oral opioids are not fast enough to control the onset of breakthrough pain. Although intravenous rescue opioids are effective for breakthrough pain, regulations in many countries like Taiwan aiming at stopping substance abuse and the diversion of medicinal opioids into illicit uses unavoidably interfere with medical availability for the relief of breakthrough pain in cancer. Breakthrough pain medications, which have relatively short duration of action such as fentanyl buccal tablet and fentanyl pectin nasal spray, were unavailable in Taiwan. The rapid onset of action of tramadol/acetaminophen and its accessibility provide a good alternative to the current breakthrough pain medications. Substantial decreases in pain scores were recorded by patients 10 min, 30 min, and one hour after the administration of tramadol/acetaminophen. There is a statistically significant improvement in pain intensity in all 3-time points ($p \leq 0.001$). The rapid-onset of analgesia provided by tramadol/acetaminophen was clinically effective. Most breakthrough pain episodes peak within 30 minutes. In this study, the mean time to pain relief was 597.2 seconds. Moreover, the analgesic effect was not related to demographics or prior opioid regimen. Only 2 cases of mild drowsiness were reported. Side effects such as nausea and vomiting that are commonly associated with the use of opioids were not observed during the treatment. Throughout the study, tramadol/acetaminophen appeared to be safe and well-tolerated. Tramadol has been known to increase the risk of seizure at high dose.[17] Acetaminophen is considered safe at therapeutic doses, but can cause fatal hepatotoxicity at higher doses.[18] In this study, patients who received high dose of opioid-based drugs, morphine with daily dose of more than 120 mg or fentanyl with daily dose of more than 50 µg/hourr, were excluded. Additional tramadol/acetaminophen based on the high dose opioids would exceed the safe dose of acetaminophen in these patients.

One of the limitations of the study is that tramadol/acetaminophen may only be effective for patients who receive weak and moderate dose of around-the-clock opioids. Tramadol/acetaminophen cannot replace strong rescue opioids when a pain gets worse and the rescue dose and frequency increase. Other limitations of this study included the lack of control arm or placebo and that it was conducted in a single medical center.

Tramadol/acetaminophen is cheaper, more readily available, and better tolerated than many widely used and highly regulated rescue medications, which include intravenous opioid analgesics and cocktails of morphine plus acetaminophen. Tramadol/acetaminophen might provide an excellent balance between efficacy, safety, accessibility, and cost-effectiveness in the treatment of breakthrough pain in cancer. Because comparison with the analgesic effects of other agents was not included in the present study. Trials which incorporate a control arm and a larger sample size are needed to further establish the efficacy of tramadol/acetaminophen in the treatment of breakthrough pain in cancer patients.

References

1. Webster LR. Breakthrough pain in the management of chronic persistent pain syndromes. ***Am J Manag Care*** 2008; 14 (5 Suppl 1): S116-S122.
2. Messina J, Darwish M, Fine PG. Fentanyl buccal tablet. ***Drugs Today (Barc)*** 2008; 44: 41-54.
3. Barkin RL. Extended-release Tramadol (ULTRAM ER): a pharmacotherapeutic, pharmacokinetic, and pharmacodynamic focus on effectiveness and safety in patients with chronic/persistent pain. ***Am J Ther*** 2008; 15: 157-166.
4. Sandrini M, Romualdi P, Capobianco A, Vitale G, Morelli G, Pini LA, et al. The effect of paracetamol on nociception and dynorphin A levels in the rat brain. ***Neuropeptides*** 2001; 35: 110-116.
5. Cavazzini F. [The combination acetominophen/tramadol in hematological daily practice]. ***Minerva Med*** 2008; 99: 631-641. Italian
6. Schnitzer T. The new analgesic combination tramadol/acetaminophen. ***Eur J Anaesthesiol Suppl*** 2003; 28: 13-17.
7. Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. ***Anesth Prog*** 2001; 48: 79-81.

8. Silverfield JC, Kamin M, Wu SC, Rosenthal N. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. ***Clin Ther*** 2002; 24: 282-297.
9. Barnett M. Alternative opioids to morphine in palliative care: a review of current practice and evidence. ***Postgrad Med J*** 2001; 77: 371-378.
10. Svendsen KB, Andersen S, Arnason S, Arner S, Breivik H, Heiskanen T, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. ***Eur J Pain*** 2005; 9: 195-206.
11. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. Breakthrough cancer pain. ***BMJ*** 2008; 337: a2689.
12. Davies AN, Vriens J, Kennett A, McTaggart M. An observational study of oncology patients' utilization of breakthrough pain medication. ***J Pain Symptom Manage*** 2008; 35: 406-411.
13. Hagen NA, Biondo P, Stiles C. Assessment and management of breakthrough pain in cancer patients: current approaches and emerging research. ***Curr Pain Headache Rep*** 2008; 12: 241-248.
14. Mishra S, Bhatnagar S, Chaudhary P, Rana SP. Breakthrough cancer pain: review of prevalence, characteristics and management. ***Indian J Palliat Care*** 2009; 15: 14-18.
15. Ruiz-Garcia V, Lopez-Briz E. Morphine remains gold standard in breakthrough cancer pain. ***BMJ*** 2008; 337: a3104.
16. Soares LG, Chan VW. The rationale for a multimodal approach in the management of breakthrough cancer pain: a review. ***Am J Hosp Palliat Care*** 2007; 24: 430-439.
17. Labate A, Newton MR, Vernon GM, Berkovic SF. Tramadol and new-onset seizures. ***Med J Aust*** 2005;182:42-43.
18. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. ***Handb Exp Pharmacol*** 2010: 369-405.

Related topics

Siddiqui AK, Mowafi HA, Al-Ghamdi A, Ismail SA, AbuZeid HA. Tramadol as an adjuvant to intravenous regional anesthesia with lignocaine. ***Saudi Med J*** 2008; 29: 1151-115.

Osifo O, Amusan TI. Outcomes of giant inguinoscrotal hernia repair with local lidocaine anesthesia. ***Saudi Med J*** 2010; 31: 53-58.

Kayali C, Agus H, Surer L, Turgut A. The efficacy of paracetamol in the treatment of ankle sprains in comparison with diclofenac sodium. ***Saudi Med J*** 2007; 28: 1836-1839.