Original Article

Controlled-Release Oxycodone Alone or Combined with Gabapentin for Management of Malignant Neuropathic Pain

Xiao-mei Li[1*], Duan-qi Liu[1], Hang-yu Wu[1], Chun Yang[2], Li Yang[3]

[1]*Department of Medical Oncology,* [3]*Departement of Medical Training, the Beijing Military General Hospital of PLA, Beijing 100700, China*
[2]*Department of Anatomy, Capital Medical University, Beijing 100069, China*

CLC number: R730.5 Document code: A Article ID: 1000-9604(2010)01-0080-07
DOI: 10.1007/s11670-010-0080-1

ABSTRACT

Objective: To evaluate the analgesic efficacy of controlled-release (CR) oxycodone and gabapentin in malignant neuropathic pain (NP).

Methods: Patients with malignant NP were enrolled and baseline pain intensity (PI) was recorded. They initially took one week CR oxycodone and were allocated to two different groups at day 8 by reevaluated PI. Patients with mild pain went to CR oxycodone mono-therapy group (OO group) and took another two weeks CR oxycodone. Others went to (CR oxycodone combined gabapentin group (OG group) and received additional gabapentin. Daily doses and side effects were recorded.

Results: Fifty-eight (92.06%) of the 63 enrolled patients completed the initial week's therapy. Twenty-two (37.93%) went to OO group and PI significantly reduced at day 15 (2.00 vs. 2.62, P=0.004), but not improved at day 22 (1.90 vs. 2.00, P=0.54). Thirty-six (62.07%) patients went to OG group and PI was significantly reduced at day 15 (4.47 vs. 2.94, P<0.001), but not improved at day 22 (2.94 vs. 2.75, P=0.136). Mean daily dose (MDD) of CR oxycodone at day 8 was 62.64 mg. It was significantly increased at days 15 and 22 (71.43 mg vs. 62.64 mg, P=0.021; 81.90 mg vs. 71.43 mg, P=0.004) in OO group. MDD of gabapentin was significantly increased at day 22 compared to day 15 (862.50 mg vs. 993.75 mg, P<0.001). Constipation was occurred in 13.64% of the patients in OO group and 14.26 % in OG group.

Conclusion: Malignant NP may be well controlled by oxycodone mono-therapy. Early combination with gabapentin is sensible when pain is not satisfactory relieved by oxycodone alone. The side effects of them are manageable.

Key words: CR oxycodone; Gabapentin; Malignant neuropathic pain; Analgesic efficacy

INTRODUCTION

Cancer pain can be effectively and safely controlled in majority of cancer patients according to the guidelines of World Health Organization (WHO). However, some cancer pain can be intractable in which neuropathic pain (NP) is a common reason. NP has been defined by the International Association for the Study of Pain (IASP) as pain that is initiated or caused by a primary lesion or dysfunction in the nervous system[1]. With few effective pharmacologic options, its treatment remains a clinical challenge. Unsatisfactory therapy of NP often leads to chronic disability, psychosocial dysfunction and familial financial disruption. Oxycodone and gabapentin have been identified as two effective analgesics in the treatment of nonmalignant NP in some randomized studies[1, 2], but they were not well studied in treating malignant NP and very few data are currently available. In China, opioids have been commonly used to relieve most moderate to severe

Received 2009−07−23; **Accepted** 2009−11−24
*Corresponding author.
E-mail: xiaomei _li@vip.sohu.com

cancer pains including cancer-related NP. The controlled release (CR) oxycodone (OxyContin tablets®, Beijing Mundipharma Pharmaceutical Co., Ltd) was not approved to treat moderate to severe cancer pain by Chinese State Food and Drug Administration (SFDA) until September 2003, but now it has already widely used in hospitals in central cities in China due to its more tolerable side effects than morphine. Up to now, however, no data of oxycodone in the treatment of malignant NP is available in our country. Gabapentin is an effective analgesic for both nonmalignant and malignant NP. In China, it has not yet been commonly used to relieve malignant NP. To provide the evidence-based options for therapy, we designed this open-label observational study to evaluate the efficacy and safety of CR oxycodone alone or combined with gabapentin for the management of malignant NP.

MATERIALS AND METHODS

This open-label observational study was conducted at the inpatient department of Medical Oncology, the Beijing Military General Hospital of PLA. Each patient gave written informed consent before participating in the study.

From June 2005 to Nov. 2008, a total of 63 consecutive cancer patients with malignant NP were enrolled into the study. Figure 1 presents the flow of the 63 patients throughout the study.

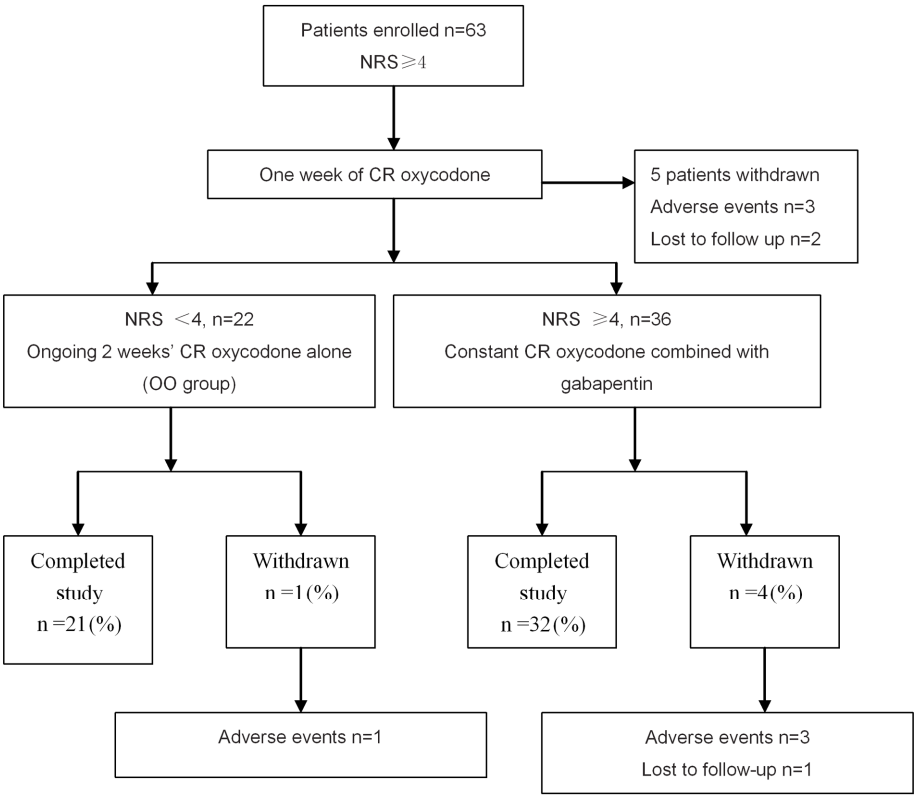

Figure 1. Flow of patients through the study.

Patients' Characteristics

Patients with moderate or severe cancer pain were enrolled if they had an active cancer lesion causing pain by infiltration or compression of nervous structures, or a neuropathy caused by chemotherapy. Patients had at least one of the following symptoms or signs referred to the pain area: burning, shooting, tingling, electrical, stabbing, pins and needles or allodynia. Imaging diagnosis (computed tomography, magnetic resonance imaging, ultrasound, or others as judged appropriate by the investigator) was required except for patients with chemotherapy-induced

peripheral neuropathy (CIPN). To these patients, a detailed description of chemotherapy directly leads to peripheral NP should be confirmed.

Inclusion and Exclusion Criteria of the Cases

Inclusion criteria were: aged 18 to less than 80 years; PI≥4 on a numerical rating scale from 0 to 10 in the 24 h period preceding the screening visit, suffered from neuropathic cancer pain as defined above; life expectancy ≥30 days; and Karnofsky performance status (KPS) ≥40.

Exclusion criteria were: unable to take medications orally; plasma creatinine >1.5 mg/ml or creatinine clearance <60 ml/min; current opioid, gabapentin, nonopioid analgesics and other adjuvant drugs use; chemotherapy from 7 d before screening throughout the study; and radiotherapy to the pain-producing lesion from 15 d before screening throughout the study. Hormone therapy could be started before the study, but the dose could not be changed afterwards. Patients were withdrawn from the study when a new pain developed or when intolerable side effects occurred during the course of the study.

Study Design

The study was divided into two consecutive phases. A baseline pain intensity (PI) was assessed by the numerical rating scale (NRS) at the screening visit (day 0) and was reevaluated at days 8, 15 and 22. In the first phase, all patients enrolled initially took one week CR oxycodone. The initial dose was 10 mg, q12h (20 mg/day) and it was carefully titrated according to patients' PI. After one week's mono-therapy, patients went on to the second phase study in which they were allocated to two different groups according to their reevaluated pain scores at day 8 and continue another two weeks therapy thereafter. Patients whose pain scores were less than 4 at day 8 were assigned to CR oxycodone mono-therapy group (OO group) in which they continued to take another two weeks CR oxycodone and gradually titrated their doses according to their pain scores. Patient whose pain scores ≥4 were assigned to CR oxycodone combined gabapentin group (OG group). In this group, CR oxycodone doses were kept constant, while gabapentin doses were administered 300 mg three times daily for patients younger than 60 years old. Initial gabapentin dose were 100 mg three times daily for patients older than 60 years old. These doses were reached slowly in three days and could be titrated to a maximum dose of 3200 mg. Side effects of CR oxycodone and gabapentin were also recorded in the study. Instant release morphine tablets were allowed every 2–4 h as needed for breakthrough pain. The rescue morphine dose should not exceeded half of the total daily opioid dose. Prophylactic bowel regimens and anti-emetics were started simultaneously with initiation of CR oxycodone therapy.

Statistical Analysis

Patients who completed at least one phase study were included into the efficacy analysis. Patients receiving at least one dose of study medications were included into the safety analysis. Patients were excluded if lost to follow up. SPSS 17.0 program was used for the analysis of data. Data were presented as $\bar{x}\pm s$. Paired t-tests were used for the comparisons of the pain scales and analgesic doses at different observational days. Statistical significance was defined as $P<0.05$ for a two-tailed hypothesis.

RESULTS

During the first observational week, 3 (4.92%) patients discontinued due to intolerable side effects of CR oxycodone. Two (3.17%) patients were lost to follow-up. Sixty-one (96.83%) patients were evaluable for the safety analysis. A total of 58 (92.06%) patients completed the first week study. During the following two weeks study, 3 (8.57%) patients in the OG group and 1 (4.55%) patient in the OO group were discontinued due to intolerable side effects. One (2.78%) patient in the OG group was lost to follow-up. A total of 53 (84.13%) patients completed the whole study (32 patients in OG group and 21 patients in OO group). Patients' characteristics are shown in Table 1.

Pain Intensity

Baseline PI of the 58 evaluable patients were 7.91(SD=1.29). It's significantly decreased to 3.74 (SD=1.11) at day 8 when they completed the initial week's CR oxycodone mono-therapy ($P<0.001$).

Twenty-two patients whose pain scales were less than 4 were allocated to OO group. Twenty-one (95.45%) patients completed the following two weeks therapy. At day 15, their mean PI significantly decreased compared to day 8 (2.00 vs. 2.62, $P=0.004$). However, it had no significant decrease at day 22 compare to day 15 (1.90 vs. 2.00,

P=0.54).

Thirty-six (62.07%) patients whose PI were ≥4 at day 8 were enrolled into the OG group and 32 patients completed the following two weeks therapy. At day 15, their mean PI were significantly improved (4.47 vs. 2.94, *P*<0.001) compared to day 8. They were continued to decrease mildly at day 22 but without statistical difference (2.94 vs. 2.75, *P*=0.14). Change in PI throughout the whole study period is depicted in Table 2.

Analgesic Doses

Mean daily dose (MDD) of CR oxycodone of all 58 completing patients at day 8 was 62.64 mg (SD=32.35), and 66.67 (SD=26.08) and 60.00 mg (SD=35.56) for OG group and OO group respectively. In OO group, MDD of CR oxycodone at day 15 was 71.43 mg (SD=26.51) and it was significantly increased compared to day 8 (*P*=0.021). At day 22, it further increased to 81.90 mg (SD=32.80) which is statistically higher than day 15 (*P*=0.004).

MDD of gabapentin significantly increased at day 22 (993.75, SD=279.33) compared to day 15 (862.50 mg, SD=282.56, *P*<0.001). MDDs of CR oxycodone and gabapentin at different observational days are listed in Table 3.

Table 1. Summary of demography and baseline characteristics-full analysis population

Parameter	Overall n=63 (%)	OG group n=32 (%)	OO group n=21 (%)
Age (y)			
Mean	57.21	57.31	57.05
SD	12.75	13.19	12.38
Min	22	22	32
Max	78	78	78
Sex (%)			
Male	33 (52)	18 (56)	9 (43)
Female	30 (48)	14 (44)	12 (57)
Tumor-related neuropathic pain			
Cervical plexopathy	3 (4.76)[a]	1 (3.13)	1 (4.76)
Brachial plexopathy	4 (6.35)	3 (9.38)	1 (4.76)
Lumbosacral plexopathy	16 (25.40)[ab]	8 (25.0)	5 (23.81)
Sacral plexopathy	12 (19.05)[b]	8 (25.0)	1 (4.76)
Monoeuropathy	7 (11.11)[b]	3 (9.38)	3 (14.29)
Central neuropathy	3 (4.76)	2 (6.25)	1 (4.76)
Neuropathic pain related to cancer therapy			
CIPN	9 (14.29)	4 (12.5)	5 (23.81)
Post-thoracotomy pain	7 (11.11)[b]	2 (6.25)	4 (19.05)
Acute herpes zoster	2 (3.17)[a]	1 (3.13)	0

[a]Lost to follow-up; [b]Withdrawn; SD: Standard deviation

Table 2. Change in mean PI throughout the three weeks study period

Day	Overall n=53	*P* value	OO group n=21(SD)	*P* value	OG group n=32(SD)	*P* value
Baseline (SD)	7.91 (1.29)		7.81 (1.25)		7.97 (1.33)	
Day 8 (SD)	3.74 (1.11)	<0.001	2.62 (0.59)	<0.001	4.47 (0.67)	<0.001
Day 15 (SD)			2.00 (0.71)	0.004	2.94 (0.67)	<0.001
Day 22 (SD)			1.91 (0.44)	0.54	2.75 (0.76)	0.14

PI: Pain intensity; SD: Standard deviation.

Table 3. Daily analgesic doses throughout the three weeks study period

Day	Daily oxycontin dose			Daily Gabapentin Dose
	Overall n=58	OG group n=32	OO group n=21	OG group n=32
Day 8				
Mean (mg)	62.64	60.00	66.67	
SD	32.35	35.56	27.08	
Min (mg)	20	20	20	
Max (mg)	180	180	120	
Day 15				
Mean (mg)			71.43[a]	862.50
SD			26.51	282.56
Min (mg)			40	600
Max (mg)			120	1800
Day 22				
Mean (mg)			81.90[b]	993.75[c]
SD			32.81	279.33
Min (mg)			40	600
Max (mg)			160	1800

[a]P=0.021; [b]P=0.004; [c]P<0.001. SD: standard deviation; Min: minimum; Max: maximum.

Safety Analysis

Of the 63 patients enrolled, 2 (3.17%) lost to follow up during the first week's study period. So, a total of 61(96.83%) patients were evaluable for the safety analysis. In addition, 3 (4.92%) patients were withdrawn due to intolerable side effects in this phase. As a result, 58 (92.06%) patients went on to the second phase study in which 1 (2.86%) patient lost to follow up in the OG group, 57 (98.28%) patients were evaluable for the safety analysis. One (4.55%) patient in the OO group and 3 (8.57%) patients in the OG group were withdrawn due to intolerable side effects. No severe side effects were observed in all evaluable patients. The most common side effect of all patients enrolled was constipation. It occurred in 13.64% patients in the OO group. The main side effects of OG group were constipation and nausea (14.26 % and 8.57% respectively). The side effects observed are listed in Table 4.

Table 4. Incidence of side effects

Side effect	1st week's oxycontin n=61 (%)[a]	OO group n=22 (%)	OG group n=35[b] (%)
Constipation	6 (9.84)	3 (13.64)	5 (14.26)
Nausea	5 (8.20)[c]	2 (9.09)	3 (8.57)
Vomiting	3 (4.92)[c]	1 (4.55)[c]	1 (2.86)[c]
Dizziness	1 (1.64)[c]	0	2 (5.71)[c]
Sedation	2 (3.28)	0	3 (8.57)
Sweating	1 (1.64)	0	1 (2.86)
Pruritus	1 (1.64)	0	0
Dry mouth	1 (1.64)	0	2 (5.71)
Asthenia	1 (1.64)	1 (4.55)	1 (2.86)
Ataxia	0	0	2 (5.71)[c]

[a]Excepted two lost to follow up; [b]Excepted one lost to follow up; [c]Withdrawn due to intolerable side effect.

DISCUSSION

Of the 63 enrolled patients in our study, 58 (92.06%) patients completed the initial week's CR oxycodone mono-therapy. Among these patients, 22 (37.93%) got a satisfactory pain control (PI decreased to mild). Twenty-one (95.45%) of these patients eventually completed the whole study and gained further pain improvement. This result indicates that some malignant neuropathic pain is responsive to oxycodone mono-therapy. If satisfactory pain relief is obtained in the initial week, ongoing titration of the same medication may be reasonable and a better pain improvement could be obtained. In addition, the analgesic doses data showed that even the daily dose of CR oxycodone significantly increased at day 22 compared to day 15 in the study, patients' mean PI were not decreased accordingly. It indicates the etiological complexity of NP and suggests coanalgesics should be considered in this phase for further pain control.

Of the 58 patients in our study who completed one week CR oxycodone mono-therapy, 36 (63.03%) patients got a significantly pain improvement compared to the baseline at day 8, but their mean PI did not reach to mild which indicated a combinational therapy should be taken. According to our study design, these patients went on to the second phase study in which they received gabapentin as a coanalgesic. Our results suggest that this combination is obviously effective. A significant difference in pain scores at day 15 compared to day 8 was observed. It indicates that this combination may be a potential effective regimen to patients whose NP were not successfully controlled by CR oxycodone mono-therapy. The early combination may be adopted and further investigation is necessary to define which type of malignant NP should be treated by the combinational therapy. Other combinations should also be studied in the future.

As to the dose of gabapentin, the titration was continued on the third week and the daily gabapentin dose increased significantly at day 22 compared to day 15, no statistically significant difference in mean PI was observed though it continued to decrease mildly. We think it may due to the fact that even the average daily gabapentin dose kept increasing during the two weeks titration, it was still far less than that of other studies[4–6]. Maybe a higher dose is more effective. However, racial differences should be considered as we found the frequency of its side effects in our study is similar to other studies[4, 7, 8]. Side effects can be another reason which limits its dose escalation. In addition, in our country, currently only 100 mg capsule gabapentin is available, this may also be an important obstacle of dose titration. As it is not only inconvenient for patients who need relatively higher doses but also causing the fear of taking so many capsules.

In terms of safety, we found that 95.08% of the 61 evaluable patients completed the initial week of CR oxycodone mono-therapy and only 3 4.92% patients had intolerable side effects. A noteworthy fact is that 4 patients receiving CR oxycodone mono-therapy (3 in the first and 1 in the second stage of the study) withdrew due to nausea, vomiting and dizziness. It indicates that even the tolerance to these side effects develops within a few days of consistent dosing, an effective regime of symptoms control should be taken until tolerance really develops. Opioid rotation may be an alternative for these patients.

In our study, the main side effect observed was constipation. It occurred in 9.84% of all the 61 evaluable patients in the first week's CR oxycodone mono-therapy and 13.64% in the OO group. The frequency of constipation in our study is similar to Fan BF and Yu SY's reports[9, 10]. The main side effects of OG group were constipation and nausea. The frequency of these side effects was similar to Hanna M's study[11] and was also similar to the OO group in this study. Unfortunately, these figures were not big enough to do further statistical comparisons. We also found a higher frequency of somnolence and dry mouth in the OG group even we can not compare them due to the same reason mentioned above. We think that the higher frequency may be the result of the side effects overlap between the two drugs. In general, both of these two analgesics are safe and most of their side effects are manageable in our study.

In conclusion, CR oxycodone is effective to malignant NP control. Some patients may gain a satisfactory pain relief by its mono-therapy. To patients whose pain is not well controlled by it alone, an early combination with gabapentin is effective. Both of the two drugs are safe and most of the side effects are readily manageable.

REFERENCES

[1] Merskey H. Logic, truth and language in concepts of pain [J]. Qual Life Res 1994; 3:S69–76.
[2] Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group [J]. J Clin Oncol 2004; 22:

2909–17.
[3] Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies [J]. Neurology 1994; 44:857–61.
[4] Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain [J]. N Engl J Med 2005; 352:1324–34.
[5] Rice AS, Maton S, Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study [J]. Pain 2001; 94:215–24.
[6] Morello CM, Leckband SG, Stoner CP, et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain [J]. Arch Intern Med 1999; 159:1931–7.
[7] Gordh TE, Stubhaug A, Jensen TS, et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study [J]. Pain 2008; 138:255–66.
[8] Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial [J]. J Pain Symptom Manage 2007; 34:183–9.
[9] Fan BF, OxyContin Tablets Postmarketing Surveillance Study Group China. Postmarketing surveillance study of OxyContin tablets for relieving moderate to severe postherpetic neuralgia pain [J]. Oncology 2008; 74:66–71.
[10] Yu SY, OxyContin Tablets Postmarketing Surveillance Study Group China. Postmarketing surveillance study of OxyContin tablets for relieving moderate to severe cancer pain [J]. Oncology 2008; 1:46–51.
[11] Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients [J]. Eur J Pain 2008; 12:804–13.