

## Efficacy and Tolerability of Cancer Pain Management with Controlled-release Oxycodone Tablets in Opioid-naïve Cancer Pain Patients, Starting with 5 mg Tablets

Wasaburo Koizumi<sup>1</sup>, Hiroshi Toma<sup>2</sup>, Ken-ichi Watanabe<sup>3</sup>, Kanji Katayama<sup>4</sup>, Masaaki Kawahara<sup>5</sup>, Kaoru Matsui<sup>6</sup>, Hiroya Takiuchi<sup>7</sup>, Kunitoshi Yoshino<sup>8</sup>, Nobuhito Araki<sup>9</sup>, Ken Kodama<sup>10</sup>, Hideyuki Kimura<sup>11</sup>, Ichiro Kono<sup>12</sup>, Hiroyasu Hasegawa<sup>13</sup>, Kaoru Hatanaka<sup>14</sup>, Kazuaki Hiraga<sup>15</sup> and Fumikazu Takeda<sup>16</sup>

<sup>1</sup>Department of Gastroenterology, School of Medicine, East Hospital, Kitasato University, Sagami-hara, Kanagawa, <sup>2</sup>Department of Urology, Kidney Center, Tokyo Women's Medical University, Tokyo, <sup>3</sup>Department of Otolaryngology, Nihon University School of Medicine, Tokyo, <sup>4</sup>First Department of Surgery, School of Medicine, Fukui Medical University, Fukui, <sup>5</sup>Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Sakai, Osaka, <sup>6</sup>Division of Thoracic Malignancy, Osaka Prefectural Habikino Hospital, Habikino, Osaka, <sup>7</sup>Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, <sup>8</sup>Department of Otolaryngology, <sup>9</sup>Department of Orthopedic Surgery and <sup>10</sup>Department of Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, <sup>11</sup>Department of Surgery, Okayama Saiseikai General Hospital, Okayama, <sup>12</sup>Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki, Okayama, <sup>13</sup>Second Department of Surgery, Tokuyama Central Hospital, Tokuyama, Yamaguchi, <sup>14</sup>Drug Safety Management Department, Shionogi & Co., Ltd, Osaka, <sup>15</sup>Department of Special Inpatient Division, National Cancer Center Hospital, Tokyo and <sup>16</sup>Comprehensive Regional Medicine, Saitama Medical School, Saitama, Japan

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**Background:** We conducted an open-label, dose titration study to assess the efficacy and tolerability of controlled-release oxycodone in the therapy of cancer pain management, starting with a newly developed 5 mg tablet every 12 h.

**Methods:** Twenty-two Japanese cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks were enrolled. The length of time and the dose needed to attain stable and adequate pain control were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.

**Results:** Eighteen patients in the efficacy population (18 out of 20, 90%) attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration. The mean length of time was 1.2 days. In these patients, the pain was significantly reduced in intensity, even at 1 h after the initial dose intake. Fifteen patients (68%) reported at least one side effect, but only one patient had to withdraw from the study because of a side effect.

**Conclusion:** The results suggest that controlled-release oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. This indicates that a lower strength controlled-release oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics.

*Key words:* oxycodone – 5 mg controlled-release tablets – titration – analgesia – cancer pain

### INTRODUCTION

Oxycodone is a semi-synthetic opioid analgesic drug that has been in clinical use for >80 years (1). It effectively relieves

both non-cancer and cancer pain in patients (2–4), and has been widely acknowledged as one of the invaluable alternatives to morphine, the parent drug of strong opioid analgesics (5,6).

The strengths of controlled-release (CR) oxycodone tablets legalized in Japan in April 2003 are 5, 10, 20 and 40 mg tablets. Since 1997, however, they have been widely available in the USA and Europe. We anticipated that a starting dose of lower than 10 mg would provide effective analgesia in cancer

For reprints and all correspondence: Wasaburo Koizumi, Department of Internal Medicine, School of Medicine, Kitasato University, 2-1-1 Asamizodai Sagami-hara Kanagawa 228-8520, Japan. E-mail: koizumi@med.kitasato-u.ac.jp

patients with moderate pain who had not previously been exposed to opioid analgesics, based on the dose ratio between morphine and oxycodone calculated in previous studies (7–10), which suggested that 5–7.5 mg of CR oxycodone would provide adequate analgesic effects comparable with those of 10 mg CR morphine tablets.

It should also be considered that a lower starting dose may be better tolerated in Japanese cancer patients with moderate pain, because the average body weight of Japanese individuals is much lower than that of Western individuals. Therefore, the starting dose of 10 mg may possibly lead to an overdose for some Japanese patients who have not been exposed to opioid analgesics previously. In addition, a lower starting dose should also be recommended for patients with renal and/or hepatic impairment in comparison with those with normal functions (11). These are the reasons why the 5 mg CR oxycodone tablets were developed to control slight to moderate pain that was not relieved with non-opioid analgesics. The tablet was also expected to be useful for cancer patients for whom a lower starting dose should be considered or a sensitive dose titration should be performed during the opioid treatment.

This was an open-label, 7 day dose titration study in cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks. The aim of this study was to determine the length of time and the dose needed for attaining stable and adequate pain control, and to evaluate the efficacy and safety of CR oxycodone tablets, with a starting dose of 5 mg every 12 h.

## SUBJECTS AND METHODS

### PATIENTS

This study was conducted over a 3 month period in adult in-patients with cancer pain recruited from 11 centers (13 divisions) in Japan. They were receiving non-opioid analgesics to manage their pain, but with little effect. The patients eligible for the study had to be cooperative, able to take oral medication and able to keep a pain diary. The patients enrolled scored their pain intensity as slight to severe pain on a 4-point categorical (CAT) scale (where 0 = no pain, 1 = slight pain, 2 = moderate pain and 3 = severe pain). They had been treated with non-opioid analgesics until entering the study, e.g. paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), but they had not taken any opioid analgesics over at least the previous 2 weeks. The values of their clinical laboratory tests for liver function (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and total bilirubin) and kidney function (serum creatinine) should not exceed the upper limit of the in-house normal reference range by more than five and six times, respectively. Patients were excluded if they had a history of hypersensitivity to opioid analgesics or if the use of oxycodone or morphine was contraindicated for any reasons. Also excluded were patients who had undergone surgery or palliative radiotherapy for pain over the previous 2 weeks,

or who were scheduled to undergo such treatments during the study period.

This study was designed mainly to assess pharmacokinetic profiles of CR oxycodone 5 mg tablet in a single dose as well as to evaluate the safety and efficacy of the CR oxycodone during the titration. For that purpose, 20 cases were considered necessary for the pharmacokinetic analysis and, therefore, we set the target number at 25 cases with the premise that there might be some cases to be excluded from the analysis set. However, in fact, we decided to discontinue the study when 22 patients were accumulated, because we judged the number of patients to be sufficient to conduct the pharmacokinetic analysis. The relationship between pharmacokinetics of oxycodone and pain intensity after the first dose will be published separately (in preparation).

All patients gave written informed consent before being enrolled in the study. The institutional review board at each center approved the protocol before the study was initiated. The study was carried out in accordance with the guideline of Good Clinical Practice (GCP) and the ethical principles originating from the Declaration of Helsinki.

### TREATMENTS

This was an open-label, dose titration study starting with a 5 mg CR oxycodone tablet given every 12 h. The initial dose was 5 mg and the dose could be titrated against the intensity of pain. If the patient reported their pain intensity as 'moderate' or 'severe' on the CAT scale, the dose could be titrated with the use of 5 and 20 mg CR oxycodone tablets every 24 h. Conversely, the doses could be reduced if the patient experienced intolerable adverse events. Dose titration against the intensity of pain was continued until a stable and adequate pain control with minimal adverse effect was obtained. We considered that adequate pain control was attained when the following conditions were fulfilled: pain-free period lasted at least 48 h; the dose every 12 h was unchanged; no supplemental analgesic dose was taken; the dosing regimen for any non-opioids or adjuvants was unchanged; the patients rated their pain intensity as 'no' or 'slight' on the CAT scale; and any adverse events were tolerable.

Throughout the study, patients were allowed to take immediate release oral morphine preparations as rescue medication whenever breakthrough pain or incident pain occurred. If patients took the rescue medication, an equivalent amount of oxycodone was added to their total daily dose of CR oxycodone tablets. The maximum daily dose of oxycodone (i.e. CR oxycodone tablets plus any rescue dose) permitted in this study was 240 mg.

Patients were not allowed to take any other opioid analgesic during the study. They were allowed to take non-opioid analgesics and adjuvant medications for their specific needs if these drugs had been given before study entry. The dose and route of administration of these drugs had to remain the same throughout the study course as they had been taking until study entry. The use of anti-side effect agents was recommended during the

study. In particular, anti-emetics and laxative agents were commonly used from study entry.

#### PAIN INTENSITY

Each day, the patients themselves assessed their pain intensity over the previous 24 h. They were also requested to assess their pain intensity at 0 h (i.e. immediately before taking their initial dose of study medication), and at 1, 3, 5, 8 and 12 h after the initial dose intake. At the same points, blood samples were collected concomitantly and assayed for plasma oxycodone and noroxycodone. They rated their pain intensity on the CAT scale described above, and on a 100 mm visual analogue scale (VAS), where 0 mm = a painless state and 100 mm = worst possible pain. Patients also recorded the number of hours that they were in pain each day and also the number of hours of sleep they had each day.

#### EVALUATION OF PAIN CONTROL AND LENGTH OF TIME TO ATTAIN STABLE AND ADEQUATE PAIN CONTROL

The investigator at each center assessed whether the patient was under stable and adequate pain control in accordance with the criteria described above. The first assessment by the investigator was made 48 h after the initial intake of the study medication. Subsequent assessment was conducted each morning until the patient had attained a stable and adequate pain control.

When the patient attained a stable and adequate pain control within the first 48 h without any dose titration, the time to stable and adequate pain control was recorded as 0 day.

#### ACCEPTABILITY OF THERAPY

Acceptability of therapy was an index based on analgesic effect and side effect of the study medication assessed by patients. Each day, the patients themselves assessed the acceptability of the therapy to them over the previous 24 h and recorded this in a diary. They rated the acceptability of therapy on the 5-point acceptability CAT scale (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). The overall assessment was done in accordance with pain intensity and the occurrence of any adverse events.

#### SAFETY ASSESSMENTS

Safety was evaluated based on the frequency and severity of adverse events, the data for which were obtained by questioning and/or examining the patients and by reviewing the patient's pain diaries and also the results of clinical laboratory tests at study entry and completion of, or withdrawal from, the study. The severity (slight, mild or severe) and seriousness (serious and non-serious) of adverse events was assessed by the investigators.

#### STATISTICAL ANALYSES

The percentage of patients who gave a rating of 'good' or 'excellent' for acceptability of therapy were analyzed

using the Clopper–Pearson method with a 95% confidence interval (CI).

Changes in the percentage of patients whose pain intensity was 'slight' and 'no' pain were assessed using the McNemar method. Changes in pain intensity (CAT scale and VAS scores) were assessed using the Wilcoxon signed rank test. The following parameters were analysed using the paired *t*-test: number of painful hours per day, number of hours sleep and acceptability of therapy ratings. The percentage of patients attaining stable and adequate pain control and the associated 95% CIs were estimated using the Kaplan–Meier method and Greenwood's method, respectively.

## RESULTS

#### PATIENT POPULATION

Of the twenty-two cancer patients enrolled in the study, 20 completed the 7 day study period. The efficacy population included 20 patients who were enrolled and did not infringe any of the inclusion or exclusion criteria. Two patients were excluded from the efficacy population because of infringement of the inclusion criteria: one patient had received a fentanyl injection (0.1 mg/day) for pain relief during biopsy 4 days before study entry; and the other patient had not been treated with any analgesic agents before the study. The safety population included all of the 22 patients who were enrolled and had received at least one dose of the study medication.

The mean age and mean body weight of all of the 22 patients were 69.1 years (range 49–80) and 54.5 kg (range 38.0–82.0), respectively. Nineteen patients (86.3%) were male. The most common diagnosis was lung cancer (25.0%), followed by stomach and esophageal cancer. The most common sites of pain were the chest and abdomen.

Two patients withdrew from the study. One withdrew because of the complication of serious pneumonia, which was not considered to be related to the study medication. The other withdrew because of somnolence, which was considered to be related to the study medication. This patient had attained stable and adequate pain control before the withdrawal.

#### TIME COURSE OF PAIN INTENSITY AFTER THE INITIAL DOSE

Table 1 shows patients' pain intensity scores (CAT scale) up to 12 h after the initial dose intake of the study medication (one 5 mg tablet). The patients' pain intensity scores decreased significantly by 1 h after the intake and the decreases continued up to 12 h after.

A similar time course of pain intensity was observed when assessed using the VAS. No patient needed supplemental medication until the next dose was given.

#### REQUIREMENTS FOR TITRATION

Eighteen of the 20 patients (90%) attained stable and adequate pain control during the 7 day study period. Table 2 shows the

**Table 1.** Changes in pain intensity up to 12 h after the initial dose

Time points (time after initial dose, h)	CAT pain intensity score*		VAS pain intensity score	
	Mean $\pm$ SD	P-value**	Mean $\pm$ SD	P-value**
0	1.7 $\pm$ 0.8	–	44.0 $\pm$ 24.8	–
1	1.3 $\pm$ 0.9	0.0078	33.0 $\pm$ 31.2	0.0022
3	1.2 $\pm$ 0.9	0.0078	32.1 $\pm$ 31.8	0.0100
5	1.0 $\pm$ 0.9	0.0020	27.1 $\pm$ 29.9	0.0016
8	1.2 $\pm$ 0.9	0.0156	31.8 $\pm$ 30.8	0.0314
12	1.3 $\pm$ 0.9	0.0469	32.1 $\pm$ 30.1	0.0285

*n* = 20 at all time points.

\*CAT pain score: 0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain.

\*\*P-value for change from 0 h after the initial dose.

**Table 2.** Mean length of time to stable, adequate pain control and mean dose needed for stable, adequate pain control\*

	Mean $\pm$ SD	Minimum	Median	Maximum
Length of time to adequate, stable pain control (days)	1.2 $\pm$ 1.9	0	0	5
Dose needed for adequate, stable pain control (mg/day)	16.7 $\pm$ 10.8	10.0	10.0	40.0

\*Patients attained stable, adequate pain control, *n* = 18.

mean ( $\pm$ SD), minimum, median and maximum length of time and the dose needed to obtain stable and adequate pain control. Mean ( $\pm$ SD) and median length of the time to stable, adequate pain control were 1.2  $\pm$  1.9 and 0 days, respectively. Mean ( $\pm$ SD) and median doses needed for stable and adequate pain control were 16.7  $\pm$  10.8 and 10 mg/day, respectively. The dose ranged from 5 to 20 mg every 12 h. Two patients were unable to attain stable adequate pain control during the study period: one withdrew because of an adverse event (pneumonia), and the other did not want to increase the study medication because of adverse events (sleepiness, itching, sweating and dry mouth). The estimated rate of achievement of stable and adequate pain control at the end of the study was 93.8% (95% CI 82.1–100.0).

Table 3 shows the number and percentage of patients who attained stable and adequate pain control at each dose level. Twelve (68%) of the 18 patients attained it at the dose of 5 mg every 12 h (10 mg/day). All of these patients required no dose titration and attained pain relief that met the criteria for stable and adequate pain control. They attained it within the first 48 h after study entry (length of time to stable and adequate pain control is 0 days).

#### CHANGE IN PAIN INTENSITY DURING THE STUDY

At study entry, 13 patients (65%) reported their pain intensity to be 'moderate' to 'severe' and seven patients (35%) reported it to be 'slight'. Table 4 shows the patient mean ( $\pm$ SD) CAT scores at study entry reported by the patients, 24 h after their

**Table 3.** Number and percentage of patients attaining stable, adequate pain control at each daily dose

Daily dose (mg)	No. (%) of patients attaining stable, adequate pain control
10	12* (68)
20	2 (11)
30	2 (11)
40	2 (11)

\*All 12 patients attained stable, adequate pain control on the first day.

initial dose intake of the study medication, and at the end of the study. The decrease in patients' pain intensity between study entry and 24 h after their first dose of study medication, and that between study entry and at the end of study were both statistically significant. Similar decreases were also observed and found to be statistically significant in making an assessment of patients' pain intensity with the use of the VAS.

The percentage of patients whose pain intensity was 'slight' and 'no' increased during the study. At the study entry, this rate was 35.0% (95% CI 15.4–59.2). The corresponding values at 24 h after the initial dose intake and at the end of the study were 70% (95% CI 45.7–88.1) and 87.5% (95% CI 61.7–98.4), respectively. The increase in the percentage of the patients whose pain was 'slight' and 'no' was statistically significant between study entry and 24 h after their initial dose intake, and between study entry and the end of the study (*P* = 0.0082).

As rescue medication, more than one dose of immediate-release morphine was used in four patients (20%) during the 7 day study period. The mean of the rescue doses per day was 1.3  $\pm$  0.5. Eighty percent of the patients required no rescue medication.

The number of hours each day that the patients were in pain decreased during the study period. At study entry, the median (range) number of painful hours per day was 12.0 h (1.0–24.0). At 24 h after the initial dose intake, it had decreased to 3.5 h (0.1–24.0), and this decrease was statistically significant (*P* = 0.0155). At the end of study, the corresponding value was 1.0 h (0.0–18.0), and this decrease from baseline (at study entry) was also statistically significant (*P* = 0.0022).

There was no change in the number of hours of sleep patients had each night during the study period. At study entry, the mean (SD) number of hours of sleep was 7.4 h (2.1). The corresponding values at 24 h after the first dose intake of the study medication and at the end of study were 7.7 h (2.3) and 7.3 h (1.9), respectively.

#### ACCEPTABILITY OF THERAPY

Figure 1 shows the acceptability of the therapy to patients at study entry and at the end of the study. At study entry, the number of patients who rated the acceptability of the therapy as 'poor' or 'very poor' was 11 (55%); at the end of the study, this decreased to 1 (5%). The change in acceptability of therapy to patients measured on a 5-point acceptability CAT scale

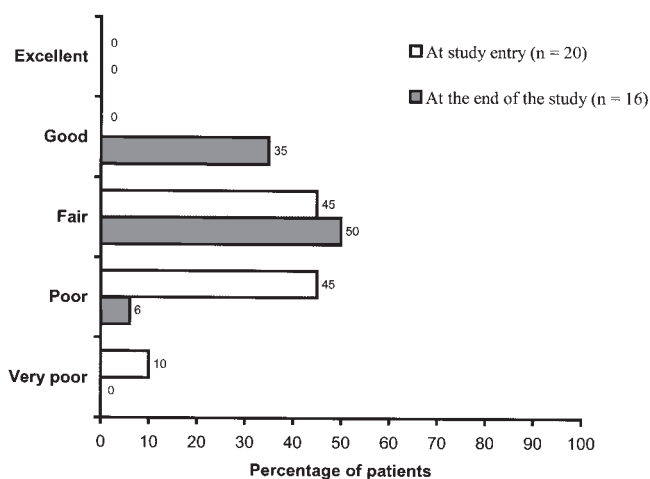
**Table 4.** Pain intensity at study entry, at 24 h after the first dose and at the end of study

	VAS pain intensity score		CAT pain intensity score		Percentage of 'slight' or 'none' patients (%)	P-value**
	Mean ± SD	P-value**	Mean ± SD	P-value**		
At study entry	47.7 ± 26.4	–	1.8 ± 0.7	–	35.0	–
24 h after first dose	28.8 ± 22.3	0.0053	1.2 ± 0.8	0.0098	70.0	0.0588
At the end of the study*	15.7 ± 16.6	0.0025	0.9 ± 0.6	0.0010	87.5	0.0082

*n* = 20 at study entry and 24 h after first dose.

\**n* = 16: at the end of the study (i.e. at 12 h after the final dose), four patients were excluded from the analysis set as "non-evaluated" cases.

\*\**P*-value for change from study entry.



**Figure 1.** Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

between study entry and at the end of study was statistically significant ( $P = 0.0024$ ).

The percentage of patients whose rating of acceptability on a 5-point acceptability CAT scale was 'good' or 'excellent' was 0% (95% CI 0–16.8) at study entry. However, at the end of study, it increased to 43.8% (95% CI 19.8–0.1).

#### SAFETY EVALUATIONS

At least one adverse event, which was considered by investigators to be at least possibly related to study medication (side effect), was observed in 15 of 22 patients (68%; 95% CI 45–86), and 41 cases occurred in total. The common (>10%) side effects were as follows: sleepiness (11 patients, 50%), constipation (seven patients, 32%), nausea (five patients, 28%) and anorexia (four patients, 18%). Most of the reported side effects were slight to moderate in severity. Six cases of severe side effects were reported. Except for one patient who had to discontinue the study due to severe somnolence, all of the patients were able to continue the treatment with the study medication in spite of the side effects. It should be noted that no serious side effects were reported.

Only one patient withdrew from the study because of somnolence that might be related to the study medication. There was no other serious side effect.

Abnormal changes either in white blood cell count or blood creatinine were seen in two patients (9%). Abnormal changes in glutamic oxaloacetic transaminase, glutamic pyruvic transaminase or positive urinary protein were seen in one patient. Changes in glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were considered to be clinically significant and considered to be related to the study medication.

Both of the clinical laboratory test values were 21 U before study entry and 51 U at the end of study. The investigator considered that it was impossible to deny the causal relationship between the study medication and the change in laboratory values, although many other drugs were used concomitantly with study medication and, therefore, the exact cause of this abnormal change in laboratory values could not be determined. These changes returned to normal after the medication was stopped.

The value of daily risk was calculated by the method of dividing the total number of incidents of seven common adverse events associated with the opioid, namely constipation, vomiting, nausea, sleepiness, dizziness, dry mouth and pruritus, by the total number of days on which the tablets were taken. The mean value of daily risk in the safety population was 0.19 (29 occurrences in 151 days). The mean value of daily risk in patients who attained stable and adequate pain control was 0.19 (23 occurrences in 125 days).

#### DISCUSSION

The World Health Organization three-step analgesic ladder has been widely used in cancer pain management (12). In many clinical settings, pharmacological treatment for mild, and sometimes moderate, cancer pain may often be initiated with non-opioid analgesic medication. It may progress to weak and then strong opioid medication in combination with non-opioid treatments as the pain increases in intensity. The only weak opioid analgesics available in Japan are codeine and hydrocodone. Their analgesic effect is due to their conversion to morphine (13) and they have a ceiling effect. This makes treatment with weak opioid analgesics inappropriate for severe cancer pain management. Hence, the strong opioids are prescribed occasionally when treatment with non-opioid analgesics is ineffective, skipping a trial of weak opioid analgesics in clinical practice. Sometimes, small doses of strong opioids, such as morphine and oxycodone, are used

instead of weaker ones in step 2 for patients who are resistant to or no longer responding to NSAIDs. On the other hand, fixed-dose combination tablets of oxycodone and acetaminophen have been used effectively as weak opioid analgesics to control mainly non-opioid-irrespective cancer pain in some countries including the USA. We thus conducted an open-label, dose titration study in Japanese cancer patients with pain who had not been taking opioid analgesics, with the starting dose of a 5 mg CR oxycodone tablet every 12 h.

Prior to this study, another study of similar design was conducted in Japanese cancer patients with pain (in preparation). Ninety-two opioid-naïve patients were enrolled in that study and the starting dose was 10 mg every 12 h (twice as high as this study). Twenty-four of 92 patients (26.1%) had to withdraw from the study within 10 days and half of them had to withdraw from the study within 2 days after the study started because of the adverse events (nausea, vomiting, sleepiness, dizziness, etc.) that are commonly associated with opioid analgesics, and most of these withdrawals (21 out of 24) occurred at the starting dose. However, 19 of the 24 patients (79.2%) reported that their pain was less than or equal to 'slight pain' on the pain score (CAT). It should be admitted that the study drug was administered without enough provisions against the side effects. However, a high incidence of sleepiness (five out of 24) and dizziness (three out of 24) associated with the study drug, which ultimately led to discontinuation of the study, suggested that the starting dose of a 10 mg CR oxycodone tablet might be too high for some Japanese cancer patients with pain who had not been taking opioid analgesics. This was possibly because the average weight of Japanese patients is less than that of Western patients.

Furthermore, since oxycodone elimination is delayed by renal (14) or hepatic impairment (15), lower dose CR oxycodone should be considered in determining the starting dose for those patients sensitive to opioids with renal or hepatic impairment. These are the main reasons for development of the 5 mg CR oxycodone tablet in Japan in addition to introduction of 10, 20 and 40 mg CR oxycodone tablets. In the present study, we tried to evaluate the clinical efficacy and safety of CR oxycodone tablets with a starting dose of 5 mg every 12 h in those Japanese cancer patients with non-opioid-irrespective pain.

Patients who still had a pain unsatisfactorily treated with non-opioid analgesics were enrolled in this study. The aim of this inclusion criterion is to include potential target patients for the 5 mg tablet. Although seven patients (35%) reported baseline pain intensity to be 'slight' at study entry on a 4-point CAT scale, we considered that these patients needed opioid therapy. This was eventually shown by the fact that none of them rated their acceptability of therapy at study entry as 'satisfactory' or 'very satisfactory' on a 5-point acceptability CAT scale. However, at the end of the study, three patients showed satisfaction with the lower dose oxycodone treatment and, moreover, there was no patient who rated their acceptability of therapy as 'poor' or 'very poor'. These results suggest that opioid therapy was indeed needed for the patients with slight pain at study entry in this study.

The 5 mg CR oxycodone tablet (a newly developed formulation) gave significant pain relief 1 h after the first dose, and the subsequent pain scores were kept significantly lower than the pre-dose scores during the following 12 h period. In addition, score for pain intensity was significantly reduced over the 24 h after the first dose intake of 5 mg of study medication as compared with that at study entry. These data indicate that the 5 mg tablet is effective for controlling cancer pain and can be administered quite safely as the starting dose for Japanese cancer patients who have not previously been taking any opioid analgesics.

In this study, 18 (90%) of the 20 patients attained stable and adequate pain control throughout the study period. Two-thirds of them did so on a dose of 5 mg every 12 h without further titration within the initial 48 h (at 0 day). The mean length of time to achieve stable and adequate pain control was 1.2 days. This result was consistent with the findings in two previous studies with CR oxycodone which showed that the mean length of time to stable and adequate pain control was 1.6–2 days (8,16). Although it is common practice to start opioid therapy with an immediate-release formulation and titrate the dose against pain intensity, Salzman and colleagues reported that CR oxycodone was also as readily titrated as an immediate-release formulation (16). Our results support their findings. Moreover, both the patients' rating of their acceptability of therapy on a 5-point acceptability CAT and the overall improvement assessment by the investigator were significantly improved at the end of this study. These results suggest that the use of 5 mg CR oxycodone tablets, if necessary with titration, is acceptable for cancer patients who had not been taking opioid analgesics and is effective for them to achieve stable and adequate pain control in a short period of time.

The 5 mg CR oxycodone tablet was developed to offer a lower starting dose for patients who might experience intolerable adverse events with a starting dose of 10 mg every 12 h. Although a high percentage of patients reported adverse events during this study, most of them were reported to be slight to moderate in severity and only one patient withdrew because of an adverse event (somnolence). Sleepiness, constipation and nausea were the three most common adverse events, all of which are widely known side effects of most opioid analgesics. Another adverse event commonly observed in this study was anorexia, which is commonly reported by cancer patients with pain and can be exacerbated by opioid administration (17).

In conclusion, CR oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. Most of the side effects were tolerable. This indicates that a lower strength CR oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics, including Japanese cancer patients who have a relatively lighter body weight, or patients with renal and/or hepatic impairment.

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