Opioid Rotation from Oral Morphine to Oral Oxycodone in Cancer Patients with Intolerable Adverse Effects: An Open-Label Trial

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Objective: We prospectively investigated the efficacy of opioid rotation from oral morphine to oral oxycodone in cancer patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or intolerable side effects.

Methods: Twenty-seven patients were enrolled and 25 were evaluated. The rate of patients who achieved adequate pain control, which provided an indication of treatment success, was evaluated as primary endpoint. The acceptability and pharmacokinetics of oxycodone were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.

Results: In spite of intense pain, the morphine daily dose could not be increased in most patients before the study because of intolerable side effects. However, switching to oral oxycodone allowed ~1.7-fold increase as morphine equivalent dose. Consequently, 84.0% (21/25) of patients achieved adequate pain control. By the end of the study, all patients except one had tolerated the morphine-induced intolerable side effects (i.e. nausea, vomiting, constipation, drowsiness). Common side effects (>10%) that occurred during the study were typically known for strong opioid analgesics, and most were mild to moderate in severity. A significant negative correlation between creatinine clearance (CCr) value and the trough concentrations of the morphine metabolites was observed. On the other hand, no significant correlation was found between CCr value and the pharmacokinetic parameters of oxycodone or its metabolites.

Conclusions: For patients who had difficulty in continuing oral morphine treatment, regardless of renal function, opioid rotation to oral oxycodone may be an effective approach to alleviate intolerable side effects and pain.

Key words: opioid rotation — morphine — oxycodone — cancer pain — pharmacokinetics

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INTRODUCTION

Oral strong opioid analgesics such as morphine and oxycodone are essential for the treatment of moderate to severe pain, irrespective of which is attributed to cancer or not (1–4).

Strong opioid analgesics have various pharmacological effects through opioid receptors, including not only analgesia but also nausea, vomiting, drowsiness and constipation, which are regarded as side effects during use for pain relief (1,2). Because of the difficulty in achieving pain relief without side effects at therapeutic dosages, appropriate treatment for side effects is necessary for a favorable balance between pain relief and side effects (1,2). In addition, when strong opioid analgesics are administered, both analgesia and side effects vary from patient to patient (1,2,5). Therefore, dose titration is required to determine the optimum dose for each patient.

The three-step analgesic ladder recommended by the World Health Organization (WHO) has been widely used in cancer pain management (1,6,7), and guidelines based on these steps have also been recommended for the treatment of non-cancer pain (8,9). However, some patients could not attain a favorable balance between pain relief and side effects because of the variability among patients in drug response (10–13). For instance, ∼10–30% of the patients who were treated with oral morphine could not attain adequate pain control (10,14). Only a few of these patients are so-called 'morphine-intolerable patients' (1), who could not utterly accept morphine, having little or no effect despite of appropriate treatment for side effects or careful dose adjustment. Even in these patients, however, 'opioid rotation' can be expected to be effective.

Opioid rotation is a method of pain management in which one strong opioid analgesic is switched to another in the treatment of chronic pain when side effects are uncontrollable and/or pain relief is inadequate despite dose titration, or for other reasons (15–18). In clinical settings, when opioid rotation is considered to be better than the appropriate treatment for side effects or careful dose adjustment, it is often adopted according to the patient's disease symptoms, response to the opioids and side effects.

With increased clinical experience in opioid rotation in recent years, opioid rotation has been increasingly recognized as an effective approach in strong opioid medication. Although the efficacy of opioid rotation has been described in various reports and reviews, many of these are based on retrospective studies, and data from prospective clinical studies have still been limited (15,19–22).

We thus conducted these prospective studies to investigate the efficacy and safety of switching from oral morphine to oral oxycodone. These opioids were selected because the WHO guideline recommends use of oral preparations for cancer pain treatment as far as possible (1), and morphine and oxycodone are the only oral strong opioid preparations currently available in Japan.

In addition to the variability in response to opioids among individuals, it is known that increase in oral morphine-induced side effects in patients with renal impairment is caused by accumulation of metabolites, particularly morphine-6-glucuronide (M6G), in the central nervous system (16,23). On the other hand, oral oxycodone-induced side effects are commonly speculated to be less influenced by renal impairment as compared with oral morphine, because the plasma concentration of the active metabolite, oxymorphone, is quite low (24,25). But no study has been conducted to investigate the pharmacokinetics of oxycodone and its metabolites following multiple doses of controlled-release oxycodone hydrochloride tablets (CR oxycodone) in patients with renal impairment, which has become a problem in actual clinical settings. We thus simultaneously conducted another study in patients with renal impairment (Study #1234) in addition to the study in patients without renal impairment (Study #1233).

Both studies were conducted in similar study patients. The study in patients with renal impairment (Study #1234) was designed to investigate the pharmacokinetics after multiple doses of CR oxycodone, but the other aspects of the two studies were similar, adopting the same study designs and major endpoints. Thus, the outcomes of efficacy and safety evaluation from the two studies were basically combined, as presented below.

PATIENTS AND METHODS

PATIENTS

The two studies (Studies #1233 and #1234) were conducted at 14 medical institutions in Japan. Patients were enrolled from February 2004 to December 2005.

The main inclusion criteria were that patients currently used oral morphine for the cancer pain treatment and had been confirmed to have difficulty in continuing oral morphine treatment. A patient was regarded to have difficulty in continuing oral morphine treatment when the patient met any of the following:

(i) At the study enrollment, the pain intensity score self-assessed on a four-point categorical (CAT) scale (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain) (26), but dose increase could not be conducted because of intolerable side effect.

(ii) The pain intensity on the CAT scale at the study enrollment was two or three (moderate or severe), but occurrence of intolerable side effects had been confirmed at previous (during seven days prior to the study enrollment) dose increase.

(iii) The pain intensity on the CAT scale at the study enrollment was one (slight pain), but at previous (during 7 days prior to the study enrollment) dose reduction to alleviate intolerable side effects, it was confirmed that pain intensity had increased to two or three (moderate or severe).

'Intolerable side effect' was defined as a persistent side effect which was intolerable for the patient despite appropriate treatments for side effects.

Other inclusion criteria were (i) inpatients aged 20 years or older who were expected to be able to take oral

medication for at least 2 weeks from the study entry and able to keep a patient diary; (ii) patients without moderate or more severe hepatic impairment (ALT and AST $\leq$2.5 times the upper limit of normal); and (iii) in Study #1233, patients without moderate or more severe renal impairment (serum creatinine (Scr) $\leq$1.5 times the upper limit of normal), or in Study #1234 patients with estimated creatinine clearance (CCr), as calculated by the Cockcroft–Gault formula from Scr levels (27), <60 ml/min.

Exclusion criteria were (i) patients with a history of hypersensitivity to opioids analgesics; (ii) patients in whom the use of oxycodone or morphine was contraindicated; and (iii) patients who had undergone surgery or a medical procedure for pain over the previous 2 weeks before the study entry or had been scheduled to undergo such treatments during the study period.

On the basis of the success rate (87%) of previous study in patients who had changed their pain treatment from morphine to oxycodone (22), it was estimated that 20 patients including withdrawal would be required to reject null hypotheses (adequate pain control rate: 50%) and accept alternate hypotheses (adequate pain control rate: 85%) by using binomial test with 80% or more power and one-side 2.5% level of significance.

STUDY DESIGN

Both studies were multicenter, open-label, dose titration studies. CR oxycodone was administered twice daily in the morning and evening as regular doses. Rescue analgesic for breakthrough pain or incident pain was immediate-release oral oxycodone powder (IR oxycodone). CR oxycodone 5 and 20 mg tablets (OxyContin®) and IR oxycodone 2.5 and 5 mg powder were supplied by Shionogi & Co., LTD. (Osaka, Japan).

The initial daily dose of CR oxycodone was individually determined based on the patient's pre-study daily morphine dose using a 3:2 conversion ratio (2,18,28). 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 or more than three times use of IR oxycodone as rescue dose within a 24-h period, the dose could be titrated with the use of 5 and 20 mg CR oxycodone every 24 h. Conversely, the doses could be reduced if the patients experienced intolerable side effects. Dose titration was continued until an adequate pain control with minimal side effect was obtained. The maximum daily dose of CR oxycodone permitted in both studies was 240 mg. The rescue dose was $\sim$1/6 of the patient's total daily CR oxycodone dose.

In both studies, titration was rated as successful, if adequate pain control was achieved within a maximum 10 days. Study #1233 was completed with achievement of adequate pain control. On the other hand, Study #1234 was completed when blood sampling for PK evaluation of oxycodone was finished on the day after achievement of adequate pain control.

No other opioid analgesics were allowed during the study. New addition of non-opioid analgesics or adjuvant analgesics for pain relief was not allowed during the study. Change in dose regimen or increase in dose of non-opioid analgesics or adjuvant analgesics was not allowed from the day before the study. Anti-side effect agents for morphine-induced intolerable side effects were allowed during the study provided they had been given on a regular basis before the study. Appropriate use of anti-side effect agents for other side effects was allowed. Patients who could attain adequate pain control within 10 days were discontinued.

In both studies, all patients provided written informed consent before the study enrollment, and the study protocols were approved by the institutional review boards at each center before the initiation of the study. Both studies were carried out in compliance with the Good Clinical Practice (GCP) guidelines and the ethical principles stated in the Declaration of Helsinki.

PK EVALUATION

In both studies, plasma trough concentrations of morphine and its metabolites were measured in patients while under oral morphine medication before the study treatment. In patients with renal impairment (Study #1234), the pharmacokinetics after multiple dosing of CR oxycodone were also investigated.

Plasma trough concentrations of morphine and its main metabolites, M3G and M6G, were measured in blood samples taken just before a regularly scheduled dosing time. Steady-state plasma concentration of oxycodone and its metabolites, noroxycodone and oxymorphone were measured in blood samples taken just before and at 1, 3, 5, 8 and 12 h after CR oxycodone dosing after achievement of adequate pain control. The PK parameters ($C_{\max}$, maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the concentration–time curve) were calculated by non-compartmental analysis using WinNonlin™ (Pharsight).

Blood concentrations of morphine, oxycodone and their metabolites were measured by validated liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS).

ENDPOINTS AND MEASUREMENTS

The primary endpoint was adequate pain control rate, i.e. the rate of patients who achieved stable and adequate pain control. Pain control was considered adequate when, over 48 h period, the dose of CR oxycodone was unchanged, the patient rated pain intensity as 'no' or 'slight' on the CAT scale, $\leq$two rescue medication per 24 h, side effects were tolerable for the patient, the dosing regimen of analgesics or adjuvant analgesics were unchanged.

The secondary endpoints included pain intensity and acceptability of therapy. Every morning, patients evaluated the mean pain intensity during the last 24 h on the CAT scale and VAS (Visual Analog Scale: 0–100 mm). At the

same time, they also rated the acceptability of the cancer pain treatment on a five-point CAT scale (1, very poor; 2, poor; 3, fair; 4, good; 5, excellent) and recorded it in their pain diaries.

Safety was evaluated daily on the basis of the frequency, severity, seriousness, causality and tolerability of adverse events. The safety data were obtained from daily clinical symptoms and clinical laboratory tests performed at the start and end of the study. The severity of adverse events was assessed in terms of three grades according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (29), i.e. Grade 1 = mild, Grade 2 = moderate, and Grade 3 or higher = severe.

STATISTICAL ANALYSES

Adequate pain control rate was analysed using the Clopper–Pearson method with two-sided 95% confidence intervals. The changes in dose, CAT, VAS, acceptability and intolerable side effects were analysed using the Wilcoxon signed-rank test. The plasma trough concentrations of morphine were analysed using *t*-tests to assess the level of significant difference between Studies #1233 and #1234.

RESULT

PATIENT POPULATION

Of 27 cancer patients enrolled in these studies (18 patients in Study #1233, 9 in Study #1234), 25 were included in the efficacy population and two were excluded: one was discontinued from the study without intake of the study medication because of worsening of a morphine-induced side effect (delirium), and the other did not meet the inclusion criteria (insufficient treatment for side effects during morphine use). Of the 25 patients in the efficacy population, four patients withdrew from the study because of inadequate pain relief in one patient, adverse event in two patients and consent withdrawn (due to non-preference for taking the rescue medication as powder formulation) in one patient. The safety population included 26 patients except for one patient who was discontinued from the study without intake of the study medication.

The detailed information on patient characteristics in the efficacy population are given in Table 1. As to renal function, which was the major difference between the two studies, Scr (mean ± SD) was lower in Study #1233 (0.7 ± 0.2 mg/dl) than in Study #1234 (1.3 ± 0.7 mg/dl). In Study #1234, to confirm the presence of renal impairment among the patients evaluated for the pharmacokinetics of oxycodone, CCr was also measured using 24 h pooled urine samples after achievement of adequate pain control. As the results, the maximum, the minimum and the mean ± SD of CCr values were 54, 16.9 and 37.2 ± 14.2 ml/min, respectively, and all patients were confirmed to have observed CCr values of <60 ml/min.

Table 1. Patient characteristics of efficacy population

Characteristic	Total (n = 25)	Study #1233 (n = 16)	Study #1234 (n = 9)
Age (years)[a]	62.8 ± 11.6	58.8 ± 10.6	70.0 ± 10.0
Gender			
Male	19	11	8
Female	6	5	1
Weight (kg)[a]	52.8 ± 7.0	52.5 ± 7.9	53.5 ± 5.5
Main inclusion criteria[b]			
a)	22	14	8
b)	0	0	0
c)	3	2	1
Primary site (>10%)			
Lung	6	5	1
Breast	3	3	0
Pancreas	3	2	1
Pain location (>10%)			
Shoulder, upper extremities	4	3	1
Chest	6	4	2
Abdomen	5	3	2
Lumbar	3	2	1
Laboratory test value for renal function[a]			
Scr (mg/dl)	0.9 ± 0.5	0.7 ± 0.2	1.3 ± 0.7
CCr (ml/min)	—	—	37.2 ± 14.2

(a) Pain intensity (CAT) was 'moderate' or 'severe', but dose increase could not be conducted because of intolerable side effect. (b) CAT was 'moderate' or 'severe', but occurrence of intolerable side effects had been confirmed at the previous dose increase. (c) CAT was 'slight pain', but an increase to 'moderate' or 'severe' had been confirmed at the previous dose reduction to alleviate intolerable side effects.
[a]Mean ± SD.
[b]Main inclusion criteria are as follows: at the study enrollment.
Scr, serum creatinine; CCr, creatinine clearance.

CHANGE IN OXYCODONE DAILY DOSE

In spite of intense pain, the morphine daily dose could not be increased in most patients before the study enrollment because of their intolerable side effects. However, switching to CR oxycodone allowed an ∼1.7-fold significant (*P* = 0.0007) increase in the morphine equivalent dose as compared with the dose just before switching by reducing the severity of side effect (Table 2).

STABLE ADEQUATE PAIN CONTROL

The adequate pain control rate, which provided an indication of treatment success, was 84.0% (21/25 patients) in total, and the length of time to adequate pain control was 2.3 days.

As detailed below, four patients withdrew from the study without achieving adequate pain control: one patient because

Table 2. Changes in CR-oxycodone daily doses

	Mean ± SD (mg)		
	Morphine daily dose	Morphine equivalent daily dose[a] (CR oxycodone daily dose)	
	Before switching	First day	Last day
Total (*n* = 24)[b]	44.4 ± 33.8	45.0 ± 33.7 (30.0 ± 22.5)	63.8 ± 40.4 (42.5 ± 26.9)

[a]Converted daily dose of CR oxycodone into morphine.
[b]One patient was excluded from calculation due to receipt of only one dose.

analgesia was inadequate; two patients due to adverse event; and one patient (not detailed below) who withdrew consent.

In the patient that withdrew due to inadequate analgesia, after switching from CR morphine 40 mg/day to CR oxycodone 20 mg/day, a morphine-induced intolerable drowsiness improved but nausea and dizziness newly developed, and no adequate pain relief could be attained in spite of dose titration, leading to discontinuation 4 days after study initiation. This patient subsequently attained pain relief after switching to transdermal fentanyl preparation and addition of NSAID and antidepressant.

Of the two patients that withdrew due to adverse events, one patient had had intolerable constipation, which persisted without improvement even after switching from a controlled-release morphine sulfate tablet (CR morphine) 60 mg/day to CR oxycodone 40 mg/day, and intolerable nausea and vomiting additionally developed. Despite careful dose adjustment, pain control was difficult and CR oxycodone was thus discontinued 3 days after study initiation. This patient subsequently attained adequate pain control after switching to continuous subcutaneous infusion of morphine.

In another patient, after switching from CR morphine 20 mg/day to CR oxycodone 10 mg/day, morphine-induced intolerable nausea and vomiting improved, but severe drowsiness newly developed, leading to discontinuation 2 days after study initiation. After switching to NSAID treatment, the drowsiness resolved and adequate pain control was attained.

PAIN INTENSITY AND ACCEPTABILITY OF TREATMENT

The results of the pain intensity self-assessments on the CAT scale showed that the mean score at the study entry was 1.9 (corresponding to 'moderate pain'), which was found to have significantly decreased to one ('slight pain') at the end of the study (*P* = 0.0001). The pain intensity on the VAS showed a similar tendency to that on the CAT scale, with a significant decrease from 53.5 mm at the study entry to 27.6 mm at the end of the study (*P* < 0.0001).

The acceptability of the treatment was assessed as 'very poor' and 'poor' at the study entry in 12 and 64% of patients, respectively, totaling ~80%. At the end of the study, however, these decreased to 8.3 and 16.7%,
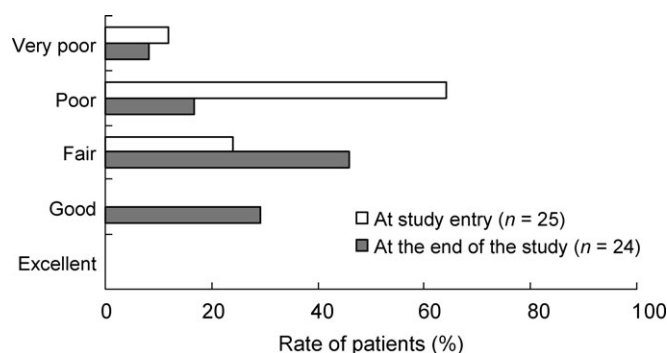
Figure 1. Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

Table 3. Number of patients with intolerable side effects

	Worst value for 7 days before the study enrollment	At the end of study	*P* value[a]
Nausea (*n* = 13)	13	0	0.0003
Vomiting (*n* = 5)	5	0	0.0253
Constipation (*n* = 5)	5	1	0.1797
Drowsiness (*n* = 7)	7	0	0.0082

[a]Paired *t*-test.

respectively, while the proportions of 'fair' (45.8%) and 'good' (29.2%) increased (Fig. 1). The mean acceptability score was 2.1 (corresponding to 'poor') at the study entry, and had significantly increased to 3.0 (corresponding to 'fair') at the end of the study (*P* = 0.0004).

CHANGE IN INTOLERABLE SIDE EFFECTS BEFORE AND AFTER THE STUDY TREATMENT

In both of these studies, morphine-induced intolerable side effects, which were the main inclusion criteria, were actually only four types, i.e. nausea, vomiting, constipation and drowsiness. During the observation period prior to the study enrollment, all patients assessed at least one of the four side effects as intolerable. At the end of the study, however, those intolerable side effects became tolerable in all patients except for one patient who had constipation (Table 3).

To confirm the change of tolerability described above, the change in severity score (0, Grade 0; 1, Grade 1; 2, Grade 2; 3, Grade 3 or higher) of each intolerable side effect before the study was compared with that at the end of the study. The mean severity scores for nausea and drowsiness were 2.3 and 2.1, respectively, during the 7-day observation period prior to the study enrollment. At the end of the study, however, the mean scores were found to have decreased to 0.4 and 0.9, respectively, with significant improvement (nausea: *P* = 0.0005, drowsiness: *P* = 0.0313). Vomiting also showed an improving tendency in severity, though without statistical significance (2.2 before the study, 0.2 at

the end of the study). Constipation showed only a slight improvement, from 2.2 before, to 1.6 at end of the study.

ADVERSE EVENTS

A total of 139 adverse events occurred among all 26 patients of the safety population. Of these, 76 adverse events in 26 patients were assessed as at least possibly related to the study medication (side effect). Common side effects ($>10\%$) were as follows: constipation in 24 patients (92.3%), drowsiness in 17 (65.4%), nausea in 13 (50.0%), vomiting in 8 (30.8%) and pruritus in 4 (15.4%). Most of the side effects were Grade 1 or 2 in severity. Severe side effects (Grade 3 or 4) occurred in six patients (6/26 patients, 23.1%), specifically: constipation in five patients, drowsiness in 3 and nausea in 1. As detailed above, two patients withdrew form the study due to side effects, one patient due to continued constipation and newly developed nausea/vomiting and one patient due to drowsiness. No death occurred during either of the studies. There was one serious adverse event of thrombocytopenia, which the investigator considered to be caused by disease progression and not related to the study medication.

Newly occurred common side effects ($>10\%$) after switching to CR oxycodone were: vomiting in five patients, drowsiness in four, nausea in four and constipation in four.

PHARMACOKINETICS

Trough concentrations of morphine and its main metabolites (M3G, M6G) were compared between the two studies (Table 4). Morphine concentrations did not significantly differ between the studies, but the concentrations of M3G and M6G were significantly higher in Study #1234, conducted in patients with renal impairment, than those in Study #1233.

In patients with renal impairment (Study #1234), significant negative correlation was observed between M6G and CCr ($P = 0.0292$). The relationship between trough concentration of M6G and CCr is shown in Fig. 2. M3G also had a significant negative correlation with CCr ($P = 0.0038$),

though no correlation was observed between morphine and CCr ($P = 0.5742$).

Pharmacokinetic profile and parameters for oxycodone, its main metabolite (noroxycodone), and active metabolite (oxymorphone) in patients with renal impairment (Study #1234) is shown in Fig. 3 and Table 5, respectively. The AUC_{0-12h} and C_{max} of oxycodone and noroxycodone were comparable. With regard to oxymorphone, however, the C_{max} and AUC_{0-12h} were very low as compared with those of oxycodone, at ~1.4 and 1.7%, respectively. In patients with renal impairment (Study #1234), no significant correlation was observed between C_{max} and AUC_{0-12h} of oxycodone or its metabolites and CCr. The relationship of C_{max} of oxycodone and its metabolites with CCr is shown in Fig. 4.
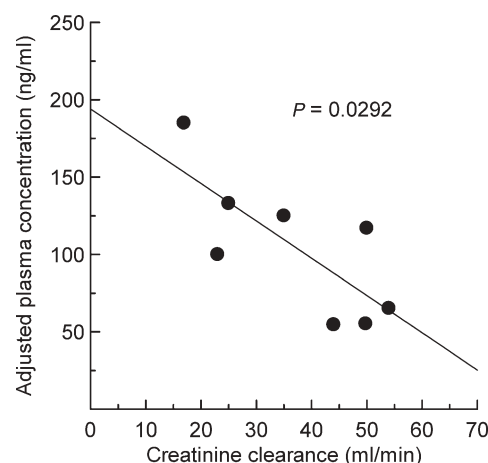
Figure 2. Results of linear regression for dependence of creatinine clearance on trough concentration of morphine-6-glucuronide (adjusted to 20 mg dose, $n = 8$).
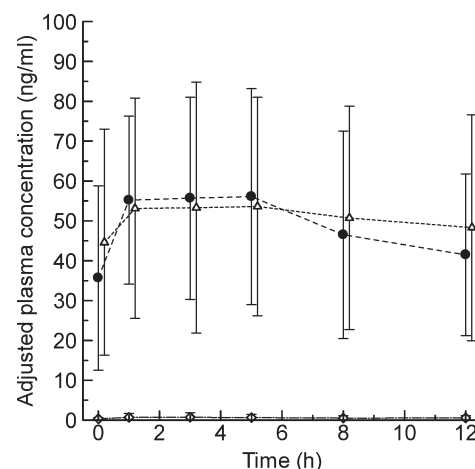
Figure 3. Mean plasma concentration profiles of oxycodone and its metabolites in patients with renal impairment (adjusted to 20 mg dose). Mean $\pm$ SD (0–8 h, $n = 7$; 12 h, $n = 5$). Filled circle, Oxycodone, open triangle, Noroxycodone; open diamond, Oxymorphone. Mean plasma concentration profiles of oxymorphone were very low.

Table 4. Comparison of trough concentration of morphine and its metabolites between patient with normal renal function (Study#1233) and patient with impaired renal function (Study#1234)

	Mean $\pm$ SD (ng/ml)		P value[a]
	Study #1233 ($n = 17$)	Study #1234 ($n = 9$)	
Morphine	10.0 ± 10.1	11.3 ± 6.4	0.7345
M3G	384 ± 332	791 ± 373	0.0088
M6G	60.0 ± 51.2	109 ± 44	0.0240

Values were adjusted to 20 mg dose. M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide.
[a]P value by t-test between 'Study#1233' and 'Study#1234'.

DISCUSSION

We conducted two prospective studies in Japanese cancer patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or occurrence of intolerable side effects in order to investigate the efficacy of the pain management regimen of switching to oral oxycodone. In particular, Study #1234 is the first study conducted to investigate pharmacokinetics of oxycodone and its metabolites at steady-state in patients with renal impairment. In these studies, 'patients who have difficulty in continuing oral morphine treatment' did not always mean 'morphine-intolerable patients' but the patients who could not have favorable pain control by morphine in actual clinical settings.

The primary endpoint in these studies was adequate pain control rate, and the rationale was that cancer pain management with strong opioids is regarded as successful only in the achievement of a favorable balance between pain relief and side effects (10,14).

For study patients who have difficulty in continuing oral morphine treatment, most of the patients could not increase morphine dose despite of intense pain because of intolerable side effects. However, switching to CR oxycodone from oral morphine allowed the dose to increase, while alleviating the side effects. As the result, an adequate pain control rate was

Table 5. Pharmacokinetic parameters of oxycodone and its metabolites following multiple administration of CR-oxycodone

	C_{max}^{a} (ng/ml)	T_{max} (h)	$AUC_{0-12h}^{a,b}$ (ng h/ml)	$t_{1/2}^{b}$ (h)
Oxycodone	61.0 ± 25.1	4.00 ± 2.52	679.0 ± 279.5	9.2 ± 2.6
Noroxycodone	57.1 ± 28.0	3.71 ± 2.21	660.0 ± 372.9	21.2 ± 10.5
Oxymorphone	0.742 ± 1.095	3.86 ± 2.97	8.19 ± 10.57	31.7 ± 20.0

Mean $\pm$ SD ($n = 7$).
[a]Adjusted to 20 mg dose.
[b]$n = 5$: Two patients could not be estimated for $AUC_{0-12\,h}$ because of missing concentration data at 12 h after CR oxycodone dosing.
C_{max}, maximum plasma concentration; AUC, area under the concentration–time curve; $t_{1/2}$, elimination half-life.

84.0% in total, or above 80% in each study. These results were comparable to those of a previous report in which success rate of opioid rotation from oral morphine to oxycodone was 87% (22), and also similar to success rates of opioid rotation between other strong opioid preparations, e.g. morphine, methadone, hydromorphone, fentanyl (64–87%) (19,20,22). High adequate pain control rate was demonstrated in Study #1234, conducted in patients with renal impairment, as it was in patients without renal impairment in Study #1233. Therefore, it is speculated that switching to oxycodone has decent efficacy in patients who had difficulty in continuing oral morphine treatment, regardless of their renal function.

The acceptability of treatment as a secondary endpoint is also an index of overall assessment of analgesia and side effects by the patients themselves. The acceptability was significantly ($P = 0.0004$) improved from the study entry to the end of the study, which is supportive of the high adequate pain control rate in these present studies. Though two patients rated the acceptability of treatment as 'very poor' (Fig. 1), these assessments were made at the time when both patients withdrew from the study because of failure to attain a favorable balance between pain relief and side effects.

The duration of the efficacy evaluation, until adequate pain control was achieved, was relatively short: $\sim$5 days. In order to investigate whether the efficacy of switching is sustained, an extension study was conducted in patients who attained adequate pain control and consented to continuation of oxycodone treatment. All the 22 patients who attained adequate pain control attended to the extension study (maximum durations of treatment were 260 days) followed by two studies. The extension study was conducted under another protocol and there was no safety issue in relation to longer administration in this study. The pain intensity was maintained around 'slight pain' on the CAT scale. This indicated that the achieved adequate pain control by CR oxycodone was maintained as favorable for long period even in patients who had difficulty in continuing oral morphine treatment (data not shown).
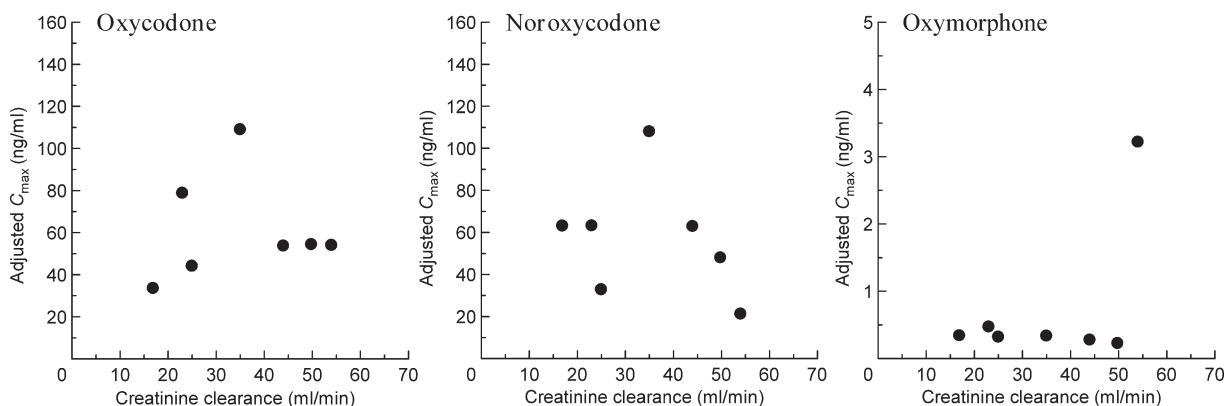

Figure 4. Results of linear regression for dependence of CCr on C_{max} of oxycodone and its metabolites (adjusted to 20 mg dose, $n = 7$).

Before study enrollment all patients had some intolerable side effect, but those side effects became tolerable at the end of the study in all patients except one patient who experienced intolerable constipation. The severity of those side effects also significantly improved, except for constipation which showed only a slight improvement. The reason was considered as follows: The severity of constipation is determined based on the types of laxatives following the NCI-CTC. Additionally, among side effects of strong opioid analgesics tolerance to constipation is known to be hard to develop (30). Therefore, there was a possibility that the unchanged severity of constipation resulted from continuing use of the same laxative agents throughout the study treatment.

Regarding constipation, there are reports that the incidence with oral oxycodone was almost equivalent to that with oral morphine (31). However, present studies suggest that switching to oral oxycodone resulted in improvement of constipation only in intolerable cases. As with other side effects, the improvement of constipation after switching to oral oxycodone may be caused by variability of response to strong opioids.

Side effects that carried over from morphine treatment and newly occurred side effects were observed in all patients after switching to oral oxycodone. However, all of these were typical of opioids and most were Grade 1 or 2 in severity. Although the number of subjects in these studies may not have been sufficient for safety evaluation, opioid rotation from oral morphine to oral oxycodone was considered unlikely to raise serious safety concerns in terms of side effects.

For pharmacokinetics of oxycodone, it has been reported that the $C_{\max}$ and AUC of oxycodone after single dose of CR oxycodone in subjects with renal impairment were $\sim$1.4 and 1.6 times higher, respectively, than those in normal subjects (32). Previously, no study has been reported regarding the pharmacokinetics of oxycodone after multiple doses of CR oxycodone in patients with renal impairment. We therefore investigated the degree of accumulation of oxycodone and its metabolites in patients with renal impairment, and compared these with the degree of accumulation of morphine metabolites.

As for morphine, the severity of renal impairment (corresponding to CCr value) showed a significant correlation with plasma concentrations of M3G and M6G, which was consistent with previous reports (31,33), thereby confirming the tendency of their accumulation. As for oxycodone, on the other hand, the severity of renal impairment had no correlation with plasma concentrations of oxycodone or its active metabolites (oxymorphone), and therefore it is considered that the concentration of oxycodone and oxymorphone may not prominently increase according to the severity of renal impairment in comparison to M6G. In fact, the $C_{\max}$ and AUC of oxycodone from this study were approximately twice as high as that from a multiple dose study in healthy patients (34,35) and increasing rate of these parameters was comparable with that from single dose study.

In patients with renal impairment, the concentration of oxycodone following multiple dose administration should show higher value to a certain degree. However, the degree of the increases of oxycodone and oxymorphone is smaller, as compared that of M6G, which is $\sim$5–6 times higher in patients with renal impairment. Moreover, the package inserts give precautions that in patients with renal impairment dose initiation should follow a conservative approach and dosage should be adjusted according to clinical situation. Therefore, we consider it is not a matter in clinical settings that patients with renal impairment receive oxycodone pain treatment with appropriate dose titration for each patient.

The present studies had some restrictions on study design due to difficult recruitment of the target patients. First, the present studies could not be conducted as randomized controlled studies. The results of the present prospective studies can be still considered quite meaningful even though these are open-label studies in a small number of patients, since many studies investigating the efficacy of opioid rotation have been retrospective.

Second, tolerability of side effects, a main inclusion criterion of the present studies, is based on subjective complaints of the patients. Since this assessment, as with pain intensity, is based on self-reported evaluation without any judgment by investigators, this assessment can be regarded as reliable only to a certain extent.

In conclusion, the results of the present studies suggested that switching to oral oxycodone from oral morphine was effective in the aspects of side effect and pain relief in Japanese patients who had difficulty in continuing oral morphine treatment because of inadequate analgesia and/or occurrence of intolerable side effects, regardless of renal function. Particularly in patients with renal impairment, it is also considered likely that the smaller increase in plasma concentration of oxycodone and its metabolites contributes to the high success rate of switching to oral oxycodone.

Conflict of interest statement
None declared.

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