

[Original Research]

Analysis of Efficacy, Safety, and Quantity of Rescue Doses of Morphine Sulfate Formulations for Cancer Pain

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Abstract: Currently, controlled-release (CR) formulations of morphine sulfate taken once a day (q.d.) are commercially available as P-GUARD™ tablets (P-tab) and KADIAN™ capsules (K-cap). However, the efficacy and safety of these drugs have not been compared yet. Therefore, we analyzed the efficacy, and quantity of rescue doses of morphine sulfate formulations for pain in head and neck cancer. The study period was between November 2005 and July 2007. We performed a crossover study on morphine dosage for 7 days in the first phase using P-tab and K-cap. The end-points were pain at rest, pain on moving, nausea, constipation, sleepiness, rescue dose, and patient/doctor evaluation. Our study subjects were divided into P-tab precedence group (10 cases) and K-cap precedence group (9 cases). There were no significant inter-group differences in the administration order effect, and administration order did not influence drug evaluation. There was no significant difference in the time effect; i.e., change before-after drug administration. Furthermore, there were no significant differences in all items of the drug effect, either. In other words, the CR morphine sulfate formulations were equal in our crossover study between groups, and consequently no significant differences were noticed in the patient/doctor evaluation. Therefore, we concluded that the opioid switch in an equi-analgesic dose of CR morphine sulfate formulations is possible.

Key words: controlled-release (CR) formulations, morphine sulfate, efficacy, safety, rescue dose

INTRODUCTION

World Health Organization (WHO) analgesic ladder¹⁾ was determined to control pain in cancer patients. When the pain reaches an advanced stage, opioids are mainly administered rather than non-opioid analgesics. Morphine has abundant formulations, such as oral tablets, injection, suppository, and conversion of morphine equi-analgesic dose is easy.²⁾ Controlled-release (CR) morphine has been the drug of choice for cancer pain, being a more convenient therapeutic regimen than immediate-release (IR) morphine.³⁾

In Japan, the commercially available formulations of CR morphine are CR morphine hydrochloride and CR morphine sulfate.⁴⁻⁶⁾ The CR morphine hydrochloride capsule contains an IR part of 20% while the characteristic CR component constitutes 80%. On the other hand, two formulations of morphine sulfate; namely, P-GUARD™ (Mitsubishi Tanabe Pharma Corporation) tablets (P-tab) and KADIAN™ (Dainippon Sumitomo Pharma Co., Ltd.) capsules (K-cap) do not include any IR component and are taken once a day (q.d.) to control cancer pain. However, the efficacy and safety of these drugs have not

been examined yet. Therefore, we administered P-tab or K-cap for head neck cancer patients who needed opioids, and comparatively examined their analgesic effect, safety, and rescue drug frequency.

A written informed consent was obtained from each participant. The study was accepted by Fukuoka University institutional ethics committee.

MATERIALS AND METHODS

1. Patients

Twenty adult patients, who had cancer pain requiring opioid analgesics, participated in the study. The patients eligible for the study had to be co-operative, able to take oral drugs, and keep a simple diary. The exclusion criteria of the patients were Eastern Cooperative Oncology Group (ECOG)^{7, 8)} Performance Status (PS) 4 and serious renal/liver damage (Table 1).

2. Study design

The study was a randomized, crossover study between P-tab and K-cap.

3. Dosage and administration

P-tab was given at bedtime q.d., K-cap was given after breakfast q.d.; the patients were randomized to receive either P-tab or K-cap for 7 days. We administered OPSO™ (morphine hydrochloride, Dainippon Sumitomo Pharma Co., Ltd.) to the patients at the time of change; i.e., the other drug was administered in turn for 7 days

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Table 1 Selection criteria and exclusion criteria

[Selection criteria]
The patient should satisfy the following selection criteria
(1) The patient older than 20 years old
(2) The patient who needs morphine newly as a general rule
(3) The patient who takes a cancer disclosure
(4) The patient who is judged by physician to have it more than 2 months
(5) The patient who can receive oral medications
(6) The patient who took it due to insufficient effect of NSAIDs
(7) The patient that provided a written informed consent to participate in the examination
[Exclusion criteria]
The patient who falls under any of the following exclusion criteria
(1) The patient with PS 4
(2) The patient with a serious renal damage
(3) The patient with a serious liver damage
(4) The patient with respiratory depression
(5) The patient during a bronchial asthma stroke
(6) The patient with acute alcoholism
(7) The patient with hemorrhagic colitis
(8) The patient who may become pregnant, during pregnancy or lactation
(9) The patient who received opioid with agreement of acquisition within 30 days

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

(Fig. 1). OPSO™ was given in a dose of approximately 1/6 of the daily dose of CR morphine.⁹⁾ As P-tab is pharmacokinetically influenced by fatty food, this drug was given at bedtime to minimize the effect of dosage time.

4. Concomitant treatment

- (1) Concomitantly prohibited drug/therapy
 - 1) New therapeutic drugs such as anticancer agent or immunotherapy
 - 2) Surgery
 - 3) Opioids except morphine and opioid antagonist
- (2) Concomitantly possible drug/therapy
 - 1) Ongoing NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) in a similar dosage as before the study
 - 2) Ongoing adjuvant drug in a similar dosage as before study (antidepressant, anticonvulsant, steroid, antiarrhythmic drug, NMDA (*N*-methyl-D-aspartate) antagonist)
 - 3) Drug/therapy necessary for adverse events of morphine
 - 4) Rescue dose of OPSO™
- (3) Increase in study drugs

The increase in the study drug means that the rescue dose frequency became >5 times a day. In that case, we followed up the patients for 1 week after the increase time.
- (4) Follow-up items and evaluation method
 - 1) Patient background

Sex, weight, age, duration of disease, with or without metastases, PS, and complication were examined. In addition, we utilized the verbal rating scale¹⁰⁾ (VRS) before the study, asking about having constipation or not, nausea/vomiting or not, degree of sleepiness, and we recorded the symptom score for each check item.
 - 2) Patient evaluation

The patients' evaluation was done after 15 days of oral

drug administration. Each patient evaluated his/her condition before the drug, recorded in their diaries each dose of the scheduled study drug, the rescue dose frequency, and adverse effects. In addition, the patients were asked to assess on a 6-point VRS their pain intensity twice each day.

- a. Pain at rest; 6-step evaluation by VRS

0=none, 1=little pain, 2=mild pain, 3=moderate pain, 4=severe pain, 5=intolerable pain
- b. Pain on moving; 6-step evaluation by VRS

0=none, 1=little pain, 2=mild pain, 3=moderate pain, 4=severe pain, 5=intolerable pain
- c. Nausea: 0=without, 1=with
- d. Sleepiness: 0=without, 1=feel sleepy, 2=sleepy
- e. Constipation: 0=without, 1=with
- f. Patient overall evaluation: 1=very satisfied, 2=satisfied, 3=unsatisfied, 4=very unsatisfied
- 3) Doctor evaluation

1=very satisfied, 2=satisfied, 3=unsatisfied, 4=very unsatisfied

The doctors referred to the patients' evaluation at the end of the study period, and assessed the patients' satisfaction concerning pain relief.

5. Statistics

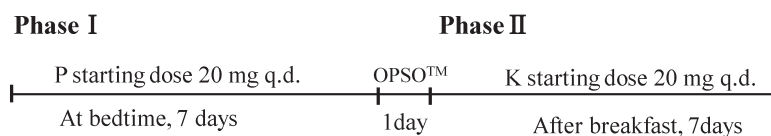
The statistical analysis was performed using the Wilcoxon signed-rank test to evaluate the administration order effect, period effect, and drug effect. Significance was set at $p < 0.05$.

RESULTS

We present the details of the patients' background in Table 2. Twenty patients enrolled in this study were randomly divided into P-tab precedence group (10 cases) and K-cap precedence group (9 cases). There was 1 case of dropout because of non-compliance.

Analysis of PS revealed PS 0 in 57.9% (11 of 19), and

P precedence group



K precedence group

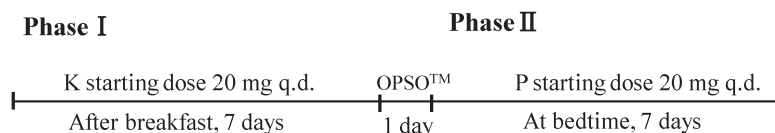


Fig. 1 Design of crossover study. P indicates P-GUARD™ tablets (P-tab), and K indicates KADIAN™ capsules (K-cap). P-tab was given at bedtime, and K-cap was given after breakfast.

PS 1 in 26.3% (5 of 19). This study was fully clinically controlled so that there would not be variation in pain control among patients. If dosage was raised, it would start from the time of dosage increase according to the protocol, but there were no such cases and the starting dose was 20 mg/day for all patients. There were no significant differences in the administration order effect, period effect, and drug effect in our crossover study. Therefore, we pooled the time and compared between the two drugs.

Analysis of the administration order effect revealed no significant differences between the groups in terms of pain at rest ($p=0.54$), pain on moving ($p=0.59$), and rescue dose frequency ($p=0.87$) (Table 3). Assessment of the side effects showed less incidence of nausea ($p=0.38$) and constipation ($p=0.14$) in the K-cap precedence group, in contrast to sleepiness ($p=0.53$) in the P-tab precedence group, but the differences were not significant. Evaluation of the K-cap precedence group revealed high patient ($p=0.14$) and doctor evaluation ($p=0.097$), but the difference was not significant.

Next, in the evaluation of the first and second phases regarding the period effect, there were no significant differences between the groups in terms of pain at rest ($p=0.12$), pain on moving ($p=0.76$), and rescue dose frequency ($p=0.23$) (Table 3). Analysis of the side effects showed a less incidence of nausea ($p=0.095$) and sleepiness ($p=0.64$) in the K-cap precedence group, in contrast to constipation ($p=0.60$) in the P-tab precedence group, but the differences were not significant.

Pain at rest ($p=0.64$) and pain on moving ($p=0.83$) were equal in the 2 groups by the drug effect after pooling the time. Regarding the side effects, nausea ($p=0.76$) and constipation ($p=0.76$) were equal, and the P-tab group showed low frequency of sleepiness ($p=0.16$). The

rescue dose frequency was similar in both groups (Table 4).

Concerning the patients' evaluation, there were 6 negative impressions which included "dissatisfaction" in the K-cap group, although 5 cases shifted to the affirmative impression "satisfaction" in the P-tab group, but the inter-group difference was not significant ($p=0.23$) (Table 5). One case was non-entry. On the other hand, regarding the negative impression "dissatisfaction," there were 3 cases in the P-tab group, but all of them shifted to the affirmative impression "satisfaction"; i.e., more than in the K-cap group.

Concerning the doctors' evaluation, there were 8 negative impressions "dissatisfaction" in the K-cap group, but 6 cases shifted to the affirmative impression "satisfaction" in the P-tab group, but the inter-group difference was not significant ($p=0.070$) (Table 6). One case remained unchanged, and 1 case was non-entry. On the other hand, 2 cases had the negative impression "dissatisfaction" in the P-tab group, but one of them shifted to the affirmative impression in the K-cap group.

DISCUSSION

Although some studies compared the efficacy and safety among formulations of opioids (morphine, oxycodone, and fentanyl),¹¹ the efficacy and safety among formulations of the oral morphine have not been analyzed yet.

K-cap (60 mg) is a CR capsule that was first marketed in 1999; having T_{max} of about 7.3 h, $t_{1/2}$ of about 9.2 h, is a sustained-release formulation to act for 24 h.⁵ On the other hand, P-tab (60 mg) is a CR tablet that was first marketed in 2005, and its T_{max} (about 4.4 h) is shorter than K-cap. It is a sustained-release formulation having a slow blood level of 27.5 h.⁶ In addition, as for P-tab,

Table 2 Patients' background

		Group		Total (%)
		P→K n=10	K→P n=9	
Sex	male	7 (70.0)	9 (100.0)	16 (84.2)
	female	3 (30.0)	0 (0.0)	3 (15.8)
Weight	<50 kg	6 (60.0)	2 (22.2)	8 (42.1)
	≥50 kg	4 (40.0)	7 (77.8)	11 (57.9)
	mean±SD	48.9±7.2	58.8±8.9	53.6±9.3
	range	35.7~59.3	45.6~72.1	35.7~72.1
Age	<60	2 (20.0)	2 (22.2)	4 (21.1)
	≥60	8 (80.0)	7 (77.8)	15 (78.9)
	mean±SD	65.5±12.4	65.6±12.3	65.5±12.0
	range	40~79	41~77	40~79
Duration of disease (month)	<3	10 (100.0)	7 (77.8)	17 (89.5)
	≥3	0 (0.0)	2 (22.2)	2 (10.5)
	mean±SD	1.0±0.6	2.9±3.9	1.9±2.8
	range	0~2	1~13	0~13
Metastases	without	4 (40.0)	2 (22.2)	6 (31.6)
	with	6 (60.0)	7 (77.8)	13 (68.4)
Performance status	0	5 (50.0)	6 (66.7)	11 (57.9)
	1	3 (30.0)	2 (22.2)	5 (26.3)
	2	1 (10.0)	1 (11.1)	2 (10.5)
	3	1 (10.0)	0 (0.0)	1 (5.3)
Complication	without	8 (80.0)	9 (100.0)	17 (89.5)
	with	2 (20.0)	0 (0.0)	2 (10.5)
Pain on moving score	0	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)
	2	1 (10.0)	4 (44.4)	5 (26.3)
	3	5 (50.0)	1 (11.1)	6 (31.6)
	4	4 (40.0)	4 (44.4)	8 (42.1)
Pain at rest score	0	0 (0.0)	3 (33.3)	3 (15.8)
	1	1 (10.0)	1 (11.1)	2 (10.5)
	2	6 (60.0)	3 (33.3)	9 (47.4)
	3	0 (0.0)	1 (11.1)	1 (5.3)
	4	3 (30.0)	1 (11.1)	4 (21.1)
Constipation	without	7 (70.0)	5 (55.6)	12 (63.2)
	with	3 (30.0)	4 (44.4)	7 (36.8)
Nausea	without	9 (90.0)	7 (77.8)	16 (84.2)
	with	1 (10.0)	2 (22.2)	3 (15.8)
Vomiting	without	9 (90.0)	7 (77.8)	16 (84.2)
	with	1 (10.0)	2 (22.2)	3 (15.8)
Sleepiness	none	6 (60.0)	6 (66.7)	12 (63.2)
	slumberous	3 (30.0)	3 (33.3)	6 (31.6)
	sleepy	1 (10.0)	0 (0.0)	1 (5.3)

P shows P-GUARD™ tablets (P-tab), and K shows KADIAN™ capsules (K-cap). P→K shows the first phase P-tab, and K→P shows the phase K-cap.

attention is necessary for delaying the dosage after meal to minimize the effect of diet due to the fatty food.

In this study, we considered the influence of diet; K-cap was administered after breakfast, while P-tab was administered at bedtime. Our crossover study was considered appropriate as the two opioids closely resemble each other, but there are some differences between the morphine formulations.

Cancer is often rapidly progressive, and therefore it may be difficult to achieve a long-term stable pain relief that is required in any crossover design. However, we coped with a wash out only in the 1st phase by

administering OPSO™, but we could not arrange the rest of drug period for ethical reasons.

Pain was well controlled during both stable phases. Of the 20 patients enrolled into the study, 19 were evaluable for safety and efficacy of the treatments. Heiskanen and Kalso¹²⁾ mentioned that even in a crossover study, the analgesic effect is influenced by the opioid administered first. Nonetheless, there was no significant difference in the dosage order effect in this study. In other words, the drug effect did not change with time; suggesting that analysis using a crossover study was possible. Next, we examined the period effect to investigate whether

Table 3 Evaluation according to the effect

Item	Group	Case	Administration order effect		Period effect		Medicine effect phase I-phase II	
			Average score	<i>p</i> -value	Average score	<i>p</i> -value	Average score	<i>p</i> -value
Pain at rest	P → K	10	7.9		10.0		7.7	
	K → P	6	9.5	<i>p</i> = 0.544	6.0	<i>p</i> = 0.117	6.7	<i>p</i> = 0.635
Pain on moving	P → K	10	9.3		10.4		9.7	
	K → P	9	10.8	<i>p</i> = 0.589	9.6	<i>p</i> = 0.764	10.3	<i>p</i> = 0.826
Nausea	P → K	5	4.6		5.0		4.5	
	K → P	2	2.5	<i>p</i> = 0.381	1.5	<i>p</i> = 0.095	3.8	<i>p</i> = 0.762
Constipation	P → K	8	9.0		6.9		7.1	
	K → P	6	5.5	<i>p</i> = 0.142	8.3	<i>p</i> = 0.596	8.0	<i>p</i> = 0.755
Sleepiness	P → K	7	5.9		7.0		5.2	
	K → P	5	7.4	<i>p</i> = 0.530	5.8	<i>p</i> = 0.639	8.3	<i>p</i> = 0.163
OPSO™ dosage	P → K	10	10.3		8.5		9.9	
	K → P	9	9.7	<i>p</i> = 0.871	11.7	<i>p</i> = 0.232	10.1	<i>p</i> = 0.944
Patients' evaluation	P → K	9	9.5		7.6		7.2	
	K → P	6	5.8	<i>p</i> = 0.136	8.6	<i>p</i> = 0.715	9.2	<i>p</i> = 0.425
Doctors' evaluation	P → K	9	9.4		7.3		6.3	
	K → P	6	5.8	<i>p</i> = 0.097	9.0	<i>p</i> = 0.525	10.5	<i>p</i> = 0.064

P indicates P-GUARD™ tablets (P-tab), and K indicates KADIAN™ capsules (K-cap). Phase I shows P → K is P-tab data, and phase II indicates P → K is K-cap data.

Table 4 Cross table of the rescue dose frequency

	During K-cap administration							Total
	0	1	2	3	4	5	6	
During P-tab administration								
0	12	2		1				15
1	2							2
2								
3								
4								
5			1					1
6							1	1
Total	14	2	1	1			1	19

Sign-test
p = 1.000

P indicates P-GUARD™ tablets (P-tab), and K indicates KADIAN™ capsules (K-cap). The vertical axis is the rescue dose frequency during the P-tab administration, and the abscissa axis is the rescue dose frequency during the K-cap administration.

examination influenced the result with time progress. We found no significant differences in all items, and the influence of time progress was denied. Furthermore, regarding the drug effect, the incidence of sleepiness was less with P-tab, but the effectiveness and safety were equal and the rescue dose frequency was similar.

As for the reason why P-tab had a good impression in the patients' evaluation and doctors' evaluation, the difference in the formulation was considered as one factor, but there were no significant differences between these groups.

In this study, P-tab and K-cap produced a stable pain control in the head and neck cancer patients. In addition,

both drugs achieved equal results in terms of administration order effect, period effect, and drug effect. Therefore, the clinical benefits of these two drugs were equal, and we concluded that the opioid switch in an equi-analgesic dose of CR morphine sulfate formulations is possible.

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Table 5 Cross table of the patients' evaluation

	K-cap patients' evaluation					Total
	Uncertain	Very satisfied	Satisfied	Unsatisfied	Very unsatisfied	
P-tab patients' evaluation						
Uncertain	3			1		4
Very satisfied			3			3
Satisfied			4	3	2	9
Unsatisfied		2				2
Very unsatisfied			1			1
Total	3	2	8	4	2	19

Sign-test
 $p = 0.227$

P indicates P-GUARD™ tablets (P-tab), and K indicates KADIAN™ capsules (K-cap).
 The vertical axis is the P-tab patients' evaluation number, and the abscissa axis is the K-cap patients' evaluation number.

Table 6 Cross table of the doctors' evaluation

	K-cap patients' evaluation					Total
	Uncertain	Very satisfied	Satisfied	Unsatisfied	Very unsatisfied	
P-tab doctors' evaluation						
Uncertain	3			1		4
Very satisfied		1	1			2
Satisfied			5	4	2	11
Unsatisfied				1		1
Very unsatisfied			1			1
Total	3	1	7	6	2	19

Sign-test
 $p = 0.070$

P indicates P-GUARD™ tablets (P-tab), and K indicates KADIAN™ capsules (K-cap).
 The vertical axis is the P-tab doctors' evaluation number, and the abscissa axis is the K-cap doctors' evaluation number.

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