Prescribing Patterns and Drug Related Problems of Opioid Analgesics and Adjuvant Medications in Patients with End-stage Cancer Receiving Palliative Care Management at a Community Hospital

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษารูปแบบการสั่งใช้ยา สาเหตุของปัญหาที่เกี่ยวเนื่องกับการใช้ยาบรรเทาปวดอนุพันธ์ฝิ่นและยาเสริมบรรเทาปวดในผู้ป่วยมะเร็งระยะสุดท้ายที่รับการรักษาประคับประคอง และความสัมพันธ์ระหว่างปัจจัยที่อาจส่งผลต่อการเกิดปัญหาที่เกี่ยวเนื่องกับการใช้ยา **วิธีการศึกษา:** การศึกษาเชิงพรรณนาเก็บข้อมูลย้อนหลังจากเวชระเบียนผู้ป่วยและแบบบันทึกข้อมูลการเยี่ยมบ้านผู้ป่วยระหว่างวันที่ 1 ตุลาคม 2558 - 30กันยายน 2559 สำรวจและประเมินปัญหาและสาเหตุที่ทำให้เกิดปัญหาที่เกี่ยวเนื่องกับการใช้ยาอิงตามเกณฑ์ The PCNE Classifications v.7.0 วิเคราะห์ข้อมูลโดยใช้สถิติเชิงพรรณนาและ Chi-square test ที่ระดับนัยสำคัญ *P*-value < 0.05 **ผลการศึกษา:** จากผู้ป่วยในทั้งสิ้น 35 ราย เป็นเพศชาย 21 ราย (ร้อยละ 60.00) อายุเฉลี่ย 61.46 ±14.98 ปี โรคที่ได้รับการวินิจฉัยมากที่สุดคือมะเร็งตับ (ร้อยละ 20.00) รูปแบบการใช้ยากลุ่มอนุพันธุ์ของฝิ่นในการควบคุมอาการปวดทั้งวันขณะนอนโรงพยาบาลที่พบมากที่สุดได้แก่ morphine MST (10) 1x2 pc พบ 5 ครั้ง (ร้อยละ25.00) ปัญหาที่เกี่ยวเนื่องกับการใช้ยาขณะนอนโรงพยาบาลเฉลี่ย 1.17 ครั้ง/ราย ซึ่งปัญหาที่พบมากที่สุด ได้แก่ Effect of drug treatment not optimal (16ครั้ง, ร้อยละ 39.02) และพบลักษณะปัญหาที่เกี่ยวเนื่องกับการใช้ยาเดียวกันดังกล่าวจากใบสั่งยากลับบ้านเฉลี่ย 1.16 ครั้ง/ราย (12 ครั้ง, ร้อยละ 54.55) การรับบริการแบบผู้ป่วยนอกเฉลี่ย 1.30 ครั้ง/ราย และจากบันทึกการเยี่ยมบ้านเฉลี่ย1.16 ครั้ง/ราย สาเหตุของปัญหาส่วนใหญ่ได้แก่ Inappropriate drug according to guidelines/formulary พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างระดับความปวดและปัญหาที่เกี่ยวเนื่องกับการใช้ยาขณะนอนโรงพยาบาล (*P*–value = 0.046) **สรุป:** พบปัญหาเกี่ยวกับการใช้ยาในผู้ป่วยมะเร็งระยะสุดท้าย ซึ่งสะท้อนความจำเป็นในการจัดการปัญหาด้านยาที่ดีโดยให้เภสัชกรมีส่วนร่วม เพื่อลดปัญหาที่เกี่ยวเนื่องกับการใช้ยาจากสาเหตุหลักที่พบและพัฒนาแนวทางการใช้ยาบรรเทาปวดและยาเสริมบรรเทาปวดอย่างสมเหตุผลในโรงพยาบาลต่อไป

คำสำคัญ: ปัญหาที่เกี่ยวเนื่องกับการใช้ยา, การดูแลแบบประคับประคอง, มะเร็งระยะสุดท้าย,ยาบรรเทาปวด, รูปแบบการสั่งใช้ยา

Abstract

Objective: To determine prescribing pattern on opioids analgesics and adjuvant medications among patients with last- stage cancer receiving palliative care. Drug related problems (DRPs) and their causes, and factors potentially associated with the DRPs were also investigated. **Methods**: In this retrospective descriptive study, patients with end- stage cancer were selected. Data were collected from inpatient medical records, outpatient medical record and home visit record for 1 year. That were explored and evaluated drug related problem by The PCNE classifications v. 7. 0 then summarized and analyzed by descriptive statistics and Chi-square test at a significance level of *P*- value < 0. 05. **Results:** There are 35 inpatients, the majority were male (21 cases or 60% of all patients) with an average age of 61. 46 ± 14. 98 years. The most diagnosed disease was liver cancer. DRPs during in hospitalization were found with an average of 1. 17 DRPs per patient. The most common DRP the effect of drug treatment not optimal (39. 02% of all DRPs). The majority cause of DRPs was Inappropriate drug according to guidelines/formulary. At out-patient visits, DRPs were found with an average of 1. 30 DRPs per patient. In home visits, an average of 1.16 DRPs per patient was found with most common cause of the effect of drug treatment not optimal. Pain level was significantly associated with having DRP during hospitalization (*P*-value = 0.046). **Conclusion:** DRPs were found among patients with terminal cancer receiving palliative care. The findings emphasized optimal medication management with pharmacist involvement. To relieve DRPs, guidelines for opioid analgesics and adjuvant medications management should developed. Such improvement could lead to a rational drug use.

Keywords: drug related problem, palliative care, end- stage cancer, analgesics, prescribing pattern

Introduction

Cancer is one of the leading causes of death worldwide.In Thailand, cancer is the third cause of death.[1] Approximately 64,000 new cancer cases were diagnosed and 30,000 deaths were reported annually. An average of 160 deaths daily was estimated. The incidence rate of cancer in Thailand was about 153. 6 per 1 0 0 ,0 0 0 population.[2] Since metastatic cancer is incurable, the role of palliative care has been increasing especially among last-stage patients.

In 2002, the World Health Organization defined last- stage patient care or palliative care as the care aiming at maintaining quality of life of both the patients facing any life- threatening illnesses and their family members. Palliative care focuses on

the suffering, either physical, psychological, social or spiritual, based on a holistic approach. The care needs to be initiated as early as the diagnosis of the terminal illness, and carried through the end of the patient's life and beyond the grief on loss among family members.[3]

When approaching the end of life, patients face distresses necessitating alleviation. Physical distresses include pain, dyspnea, lethargy, loss of appetite, nausea, vomiting, constipation, insomnia and confusion. Given patients may face more than one physical distress simultaneously. [4] Opioid derivatives have been helpful in alleviating distressful symptoms in last-stage patients especially those with severe pain. With their actions on specific pain receptors, opioid derivatives could inhibit pain through the ascending pain pathway. Even with a promising pain relief, opioid derivatives are not free of some significant adverse effects including respiratory depression. Another side effect not always relating to dose of opioid derivatives is constipation. This is because opioid derivatives decrease intestinal water reabsorption, secretion and motility.

In selecting appropriate analgesics for end-stage patients, pain severity dictates drug choices. In addition to pain relief, adjuvant medications for specific causes of pain are also recommended. For example, patients with neuropathic cancer pain are given tricyclic antidepressant such as amitriptyline and nortriptyline concomitantly with pain killers. In last-stage cancer patients with dyspnea, benzodiazepines such as diazepam and lorazepam are recommended.[5]

In an international study on prescribing pattern among cancer patients, strong opioid derivatives were prescribed in as high as 61% of the patients during the last three months of their lives.[6] In Thailand, the problems of opioid derivative use have been multi-facet. Thailand has been recognized as the country with low use of morphine. The patients in need of morphine are those with cancer, and severe toothache or headache. Unfortunately, among 65% of the patients who needed morphine, only 20% of them received morphine prescription. Since morphine is a schedule-2 narcotics in Thailand, its distribution has always been subject to a strict legal scrutiny. With no domestic production of opium in Thailand, all opioid derivatives have to be imported. All parties face challenges along the whole distribution process including complicate purchasing steps, delayed distribution, and supply running out due to the restriction on borrowing or exchanging products between hospitals. Moreover, strict rules on opioid derivative use have feared healthcare providers to deal with the products.[7]

With a relatively limited number of drug items in hospital formulary compared to higher level hospitals, community hospitals face the most troublesome morphine supply shortage.This usually causes the patients and family members time and expense to get a referral for opioid drugs at provincial hospitals. Unfortunately, only a limited amount of prescribed drugs were allowed, for example, a one-week or one-month supply of regular morphine tablets and a 30-tablet supply of controlled-release morphine tablets. Patients with devastating stage of illness or unable to pay a visit to the provincial hospitals remained in pain with the shortage of opioid drug supply.[8]

To alleviate the access problem, region 7 office of the regional healthcare system consisting of the four provinces of Konkaen, Mahasarakham, Kalasin and Roi-et has developed a program to enhance the access to opioid derivative analgesics for last-stage patients. All four provincial hospitals have engaged in the program as the network nodes for all community hospitals in their provinces. Development included referral system for last-stage patients, pharmacist's performance on drug distribution and multidisciplinary teamwork in palliative care.

Khaowong Hospital, a 60-bed community hospital in Kalasin province, is responsible for patients in the districts of Khaowong and Nakoo of Kalasin, and certain parts of districts of Bankaw, Kamcha-ee, and Dongluang of Mukdaharn province. End-stage patients in these areas have been under the continuous palliative care of Khaowong Hospital in their residential communities. Under the provision of the center for continuous care for end-staged patients, a multidisciplinary team consisting of physician, nurse, pharmacist, public health technical officer and physical therapist, was formed in 2013. More end-stage patients had been taken care of since 2014. Despite an existing guideline for palliative care for the team to follow, certain problems remained especially drug related ones. With no guideline to specifically handle drug related problems (DRPs) among opioid analgesics and other drugs necessary for end-stage cancer patients, pain and distress management for these patients was insufficient. Such shortcoming had had certain portion of patients suffered greatly.

Based on a routine-to-research study at Khaowong Hospital, there had been an increase in the use of opioid

analgesics in patients with terminal cancer.[9] As a result, more DRPs arising from these analgesics were inevitable. These DRPs included disrupted prescriptions of opioid analgesics resulting in no supply of analgesics for continuous pain control (around-the-clock dosing) and/or for breakthrough pain. A problem of analgesics dosing not in agreement with pain level was also relatively prominent, if not prevalent. For example, patients with a pain score of only 2 to 3 out of 10 were given morphine which is a potent opioid analgesics. Patients also suffered from adverse effects of analgesics including constipation, dry mouth, and dry throat. Other DRPs included the need for medications to relieve side effects caused by analgesics. For example, laxative drug was not given to alleviate constipation caused by opioid analgesics.

A study at Jaokunpiboonphanomtuan Hospital to examine the effect of pharmacist participation in providing multidisciplinary care to cancer patients found that the number of DRPs of 1.46 DRPs per patient at baseline was reduced to 0.47 DRPs per patient post-intervention.[10] Pharmacist involvement in the multidisciplinary team allowed for effective identification and dissolution of DRPs. It was also found that patients and healthcare providers were satisfied with pharmacist participation in the care process. It was obvious that there has been a relative lack of studies to determine the extent of DRPs of analgesics and related adjuvant medications in patients with terminal cancer requiring palliative care. Causes of such DRPs were also not fully understood. This present study aimed to determine 1) prescribing patterns of analgesics and adjuvant medications in patients with terminal cancer, 2) the causes of such DRPs, and 3) relationships between potential factors and the DRPs, at Khaowong Hospital. The findings could be useful in improving the guideline regarding analgesic management in the multidisciplinary team.

Methods

In this retrospective study, patient data from October 1, 2015 to September 30, 2016, were collected medical records of in-patient, out-patient, and home healthcare visits. Patients were those with terminal cancer receiving palliative care provided by Khaowong Hospital and they were recruited into the study based the following inclusion criteria. They needed to be diagnosed with terminal cancer, at least 18 years of age, receiving palliative care, and given at least one type of opioid analgesics and adjuvant medications available in Khaowong Hospital. These analgesics included 10-mg sustained release morphine sulfate tablets (or MST), morphine injection (10 mg/amp.), morphine syrup (10 mg/5mL), tramadol injection (50 mg/amp.), 50-mg tramadol capsule, and pethidine injection (50 mg/amp.). Adjuvant medications were 0.5-mg lorazepam tablet, 2- and 5-mg diazepam tablet, diazepam injection (10 mg/amp.), 10-mg nortriptyline tablet, and 10- and 25-mg amitriptyline tablet. Other medications included laxatives such as bisacodyl tablet, milk of magnesia, and lactulose. To be eligible, the patient's medical records either from hard copy or electronic records (HosXP®) needed to be sufficient for analysis. Patients were excluded if they received treatment modalities other than analgesics. These treatments included physical therapy, acupuncture, and alternative medicine. All 63 patients in the registry of palliative care were verified for eligibility. All eligible patients were subject to inclusion. No sample size justification was performed since there was a small number of patients in the registry.

Study instruments

In terms of study instruments, a set of questionnaires was used to collect data of demographic information and medication use. Clinical status was also assessed as follows. Pain was measured using the numerical rating scale (Pain score; PS) and categorized into three levels, i.e., patients with severe pain (PS of 7 – 10 points), moderate pain (PS of 4 – 6 points), and mild pain (PS of 1 – 3 points).[5] The patient's performance was assessed using the Palliative Performance Scale (PPS) for Adult Suandok. Five dimensions of palliative performance included ambulation, activity/extent of disease, self-care, intake, and consciousness level. The performance was categorized into stable (PPS of 70 - 100%) and terminal (PPS of 0 - 30%), and those in between the two categories (PPS of 40 - 60%).[11] DRPs were identified according to the Pharmaceutical Care Network Europe (PCNE) classifications v.7.0.[12] Treatment modalities and medication use were based on the clinical practice guideline for cancer pain (2013) of the Thai Association for the Study of Pain[5] and clinical practice guideline of palliative care (2014) of the Department of Medical Services, Ministry of Public Health.[4] To identify DRPs and the related causes, pharmacist in the palliative care of Khaowong Hospital was responsible for the task with discussion with the expert clinical pharmacists to reach the sensible agreement.

Data collection

Data of eligible patients on their last hospitalization during October 1, 2015 to September 30, 2016 were collected. Data after discharge, to the out-patient and home healthcare visits were also collected. This study was approved by the Human Ethics Committee of Mahasarakham University (Issue No. 19/2560, March 6, 2017).

Data analysis

Data of demographic and clinical status including gender, age, payment scheme, caregiver, diagnosed illnesses, co-morbidities, and hospitalization days, were summarized using descriptive statistics. Categorical variables were test for relationship using chi-square test. Statistical significance was set at a confidence level of 95% (*P*-value < 0.05). All statistical analyses were performed using SPSS software program version 16. 0. We tested the relationships between independent variables (gender, age groups, co-morbidity groups, pain levels and PPS groups) and dependent variables (DRPs).

Results

Of the 63 patients in the registry, 35 of them were eligible. Of the 28 patients excluded, 14 were diagnosed with diseases other than terminal cancer, nine were not hospitalized within the study duration, 3 did not have in-patient medical records, 1 was younger than 18 years old, and 1 was treated with alternative medicine.

The majority of the 35 participants were men (60.00%) (Table 1). Their age was 61.46 ± 14.98 years by average. Most of them had universal coverage payment scheme (80.00%) and all of them had caregivers. The majority had liver cancer (20.0%) and had at least one co-morbid disease (45.71%) with 25.71% having anemia. Type of pain was assessed in 14 patients (40. 00% 0 while pain level was evaluated in 28 patients (80.00%). Twelve of 28 patients (42.86%) were found to have severe pain (PS of 7 – 10 points). PPS was assessed in 19 patients (54.29%). The majority (12 of 19 patients, or 63.16%) were within the PPS of 40 – 60%. Two patients had dyspnea. Average hospitalization was 4.49 days per patient. There were ten patients who had out-patient visits after the discharge; while six patients had home healthcare visits.

Table 1 Demographic and clinical status information of the participants (N = 35).

Patient information	No. (%)
Gender	
Male	21 (60)
Female	14 (40)
Age (mean = 61.46 ± 14.98 yrs)	
18 – 60 yrs	25 (71.43)
61 yrs or older	10 (28.57)
Payment scheme	
Universal coverage	28 (80)
Civil servant scheme	7 (20)
Marital status	
Married	34 (97.14)
Single	1 (2.86)
Diagnosed illnesses	
Liver cancer	7 (20.00)
Lung cancer	6 (17.14)
Bile duct cancer	5 (14.28
Colon cancer	4 (11.42)
Cervical cancer	2 (5.17)
Other*	11 (31.43)
Number of co-morbid disease	
0	19 (54.29)
1	9 (25.71)
2	5 (14.28)
3 or more	2 (5.71)
Pain level based on pain score (PS) (n = 28)	
Severe pain (PS of 7 – 10 points)	12 (42.86)
Moderate pain (PS of 4 – 6 points)	8 (28.57)
Mild pain (PS of 1 – 3 points)	5 (17.86)
No pain (PS of 0 points)	3 (10.71)
Palliative performance score (PPS) and level (n = 19)	
Stable (PPS of 70 - 100%)	3 (15.79)
Middle (PPS of 40 - 60%)	12 (63.16)
Terminal (PPS of 0 - 30%)	4 (21.05)
Number of hospitalization days	
1 - 5	25 (71.43)
6 or more days	10 (28.57)
Types of discharge	
With physician permission	24 (68.57)
Treatment denied	6 (17.14)
Referral to other hospital	5 (31.42)

* Other kinds of cancer: one case (2.85%) for breast cancer, gastric cancer, lymphnode cancer, muscle cancer, gallbladder cancer, brain cancer, saliva gland cancer, ovarian cancer, intestinal cancer, adrenal gland cancer, and urinary bladder cancer.

Prescribing patterns during hospitalization and after discharge

Of the 35 patients hospitalized, 20 of them were prescribed around-the-clock dosing of analgesics for continuous pain control (Table 2). The most prescribed around-the-clock opioid analgesics were 10-mg morphine tablets (or 10 mg MST) 1x2 pc (5 of 20 patients, or 25.00%). For breakthrough pain, the most prescribed analgesics were morphine injection (3 mg iv prn q 4 hr) (7 of 25 patients, or 25.92%). For adjuvant medications, lorazepam was prescribed in 9 of 35 patients (25.71%).

In terms of medication adjustment, of a total of 20 adjustments, frequency adjustment was found the most (11

adjustments or 55.00%). For example, morphine injection 3 mg iv q 6 hr was changed to morphine injection 3 mg iv q 4 hr. Dose adjustment was done two times (10.00%). For example, morphine injection 3 mg iv q 4 hr was changed to morphine injection 10 mg iv q 4 hr.

Table 2 Prescribing patterns during hospitalization and at discharge (N = 35).

Prescribing patterns of opioid analgesics	No.	%
1) During hospitalization		
• Opioid analgesic prescription for continuous control (around-the-clock dosing)		
No	15	42.86
Yes	20	57.14
Dosing regimens prescribed[a]		
Morphine MST (10 mg tab) 1 x 2 pc	5	25.00
Morphine MST (10 mg tab) 1 tab q 12 hr	3	15.00
Morphine injection 3 mg iv q 6 hr	2	10.00
Morphine injection 4 mg iv q 6 hr	2	10.00
• Opioid analgesic prescription for breakthrough pain		
No	9	25.71
Yes	26	74.29
Dosing regimens prescribed[b]		
Morphine injection 3 mg iv prn q 4hr	7	25.92
Morphine injection 3 mg iv prn q 6 hr	4	14.81
Morphine injection 3 mg iv prn q 8 hr	4	14.81
• Adjuvant medications		
No	25	71.43
Yes	10	28.57
Dosing regimens prescribed		
Lorazepam (0.5 mg tab) 1 x hs	8	88.89
Lorazepam (0.5 mg tab) 2 x hs	1	11.11
2) At discharge		
• Opioid analgesic prescription for continuous control (around-the-clock dosing)		
No	16	45.71
Yes	19	54.29
Dosing regimens prescribed[C]		
Morphine MST (10 mg tab) 1x3 pc	5	27.78
Morphine MST (10 mg tab) 1 tab q 12 hr	2	11.11
Morphine injection 2 mg iv prn q 4 hr.	1	5.55
Morphine injection 5 mg iv prn q 6 hr.	1	5.55
• Opioid analgesic prescription for breakthrough pain		
No	14	40.00
Yes	21	60.00
Dosing regimens prescribed[d]		
Morphine syrup 3 mL q 2-4 hr.	3	21.43
Morphine injection 3 mg iv prn q 4 hr	2	14.28
Morphine syrup 2 mL q 2-4 hr	1	7.14
• Adjuvant medications		
No	24	68.57
Yes	11	31.43
Dosing regimens prescribed[e]		
Lorazepam (0.5 mg tab) 1 x hs	8	72.73
Nortriptyline (10 mg tab) 1 x hs	1	9.09

[a] Other dosing regimens prescribed for continuous pain control during hospitalization included morphine 6 mg iv q 6 hr, morphine 4 mg iv q 8 hr, morphine 4 mg iv q 12 hr, MST 10 mg 1 tab q 8 hr, MST 10 mg 2 x 2 pc, with one prescription each.

[b] Other dosing regimens prescribed for breakthrough pain during hospitalization included morphine 2 mg iv prn q 4 hr, morphine 3 mg iv prn , tramadol 50 mg iv prn q 8 hr, pethidine 25 mg iv q 6 hr, morphine syrup 3 ml prn q 2-4 hr, morphine syrup 5 ml prn q 2 - 4 hr, and morphine syrup 2.5 ml prn q 2 - 4 hr, with one prescription each.

[c] Other dosing regimens prescribed for continuous pain control at discharge included morphine 5 mg iv prn q 8 hr, morphine 10 mg iv prn q 4 hr., tramadol (50) 1x3 pc, MST (10) 1 tab q 8 hr, MST (10) 4 tab q 12 hr, MST (10) 9 tab q 8 hr, and MST (10) 1x2 pc, with one prescription each.

[d] Other dosing regimens prescribed for breakthrough pain at discharge included morphine syr. 5 ml prn q 2 hr, morphine syrup 20 ml q 2 - 4 hr, morphine syrup 2 ml x 2 pc, and morphine injection 2 mg iv prn q 4 hr, with one prescription each.

[e] Other adjuvant medicatons prescribed at discharge included lorazepam 0.5 mg 2 x hs, and diazepam 5 mg iv prn, with one prescription each.

In terms of medications prescribed at discharge, 19 of 35 patients were given around-the-clock analgesics (54.29%). The most prescribed analgesic regimen was morphine MST 10 mg 1 tab X 3 pc (5 of 19 patients, or 26.32%). For breakthrough pain, analgesics were prescribed in 14 patients (40.00%) where morphine syrup 3 mL q 2 - 4 hr was the most prescribed regimen (3 of 14 patients, or 21.43%). A regimen of morphine syrup 5 mL prn q 2 hr was also prescribed. It was found that 11 patients were given adjuvant medications at discharge where a regimen of lorazepam 0.5 mg tablet 1 x hs was prescribed the most (8 of 11 patients, or 72.73%).

After discharge, 10 of 35 patients (28.57%) returned for out-patient visits with an average of 2.5 visits per patient. For pain level, four patients were evaluated and all had a severe pain (PS of 7 – 10 points). Only three patients were assessed for palliative performance. One patient had a PPS score of 90% at hospitalization which decreased to 60% at discharge; while that of another patient decreased from 40% to 30%.

After discharge, 9 of 10 patients returing for out-patient visits were prescribed around-the-clock analgesic regimen (90.00%). Prescribed regimens included morphine MST 10 mg 1 tab q 8 hr and morphine injection 10 mg iv q 4 hr. For breakthrough pain relief, four patients were given analgesics (40.00%), such as morphine syrup 2 ml prn and morphine injection 10 mg iv q 4 hr. Regimen adjustment was found in two patients; one with medication change and another with dose change. Adjuvant medication was prescribed only for one patient with the regimen of lorazepam tab 0.5 mg 1 x hs. In terms of adverse effects, two patients experienced constipation.

After discharge, six patients were followed up with **home healthcare visits** with an average of 1.16 visits per patient. At home visits, severe pain (PS of 7 – 10 points) was found in four patients, moderate (PS of 4 – 6 points) and mild (POS of 1 – 3 points) in one patient each. Palliative performance was evaluated in all six patients where three patients were in the three in ternal level (PPS of 0 - 30%) while the other three were in the level between stable and terminal level (PPS of 40 – 60%). Various distresses were found including restlessness, slurred speech, hematuria, confusion and weakness. Few patients self-adjusted dose of opioid analgesics.

Drug related problems and associated causes

During **hospitalization**, 41 DRPs were found with an average of 1.17 DRPs per patient. According to the Pharmaceutical Care Network Europe (PCNE) classifications

v.7.0, the most found DRP was P1.2 Effect of drug treatment not optimal (P1.2) (16 of 41 DRPs, or 39.02%) (Table 3). The most found cause of such DRP was C1.1 Inappropriate drug according to guideline/formulary. For example, patients with persistent pain were not given around-the-clock dosing of opioid analgesics and patients with breakthrough pain were not given rescue opioid painkiller injection.

Table 3 Drug related problems (DRPs) and associated causes during hospitalization according to PCNE v.7.0 (N = 41).

Problem code	No. (%)	Cause code	No. (%)	Example of DRP causes
P1.2	16 (39.02)	C1.1	7 (43.75)	- Patients with persistent pain were not given around-the-clock dosing of opioid analgesics. - Patients with breakthrough pain were not given rescue opioid painkiller injection.
		C8.2	4 (25.00)	- Patients experienced sedation (sedation score of 3) after morphine injection. - Patients experienced breakthrough pain since no around-the-clock analgesic drug was prescribed.
		C3.3	2 (12.5)	- Patients with persistent pain, but was given morphine injection q 6 hr which was not adequately frequent. - Patients were unable to control pain after morphine injection and the frequency of analgesic drug was not adjusted according to pain level.
		C6.2	2 (12.5)	- Around-the-clock morphine injection was prescribed, but was given PRN as recorded by the nurse. - Uncontrolled pain and analgesic drug administration was recorded as less frequently than prescribed (4 mg iv q 8 hr).
		C2.1	1 (6.25)	- Patients were unable to swallow and needed NG tube but MST should not be splitted, ground or chewed to avoid a loss of therapeutic effect.
		C3.1	1 (6.25)	- Dosage of analgesics was too low and breakthrough pain frequently occurred.
		C3.2	1 (6.25)	- Dose of morphine syrup was more than 10% of the around-the-clock dose.
P2.1	8 (19.51)	C1.8	7 (87.5)	- Patients experienced constipation from MST but laxative drug was not prescribed.
		C8.2	1 (12.5)	- Patients experienced constipation from MST and the symptom persisted despite milk of magnesia was given.
P3.2	6 (14.63)	C3.4	2 (33.33)	- Physician prescribed MST 1 tab q 4 hr.
		C8.1	2 (33.33)	- With no assessment after morphine injection, effectiveness of PRN morphine was not known.
		C8.2	1 (16.66)	- Detail of morphine syrup administration was not recorded. - Morphine injection was changed to MST by physician, but the dose was as high as 230% of usual dose and no assessment was done after regimen adjustment.
		C5.1	1 (16.66)	- Senokot® was prescribed but the item was not available in the hospital.
P1.3	5 (12.20)	C1.5	5 (100.00)	- Both morphine injection and morphine syrup were prescribed concomitantly. - Pethidine was prescribed concomitantly with MST.
P1.1	4 (9.76)	C1.1	3 (75.00)	- Around-the-clock analgesic drug was not prescribed. - Breakthrough pain was poorly controlled, but no dose adjustment was made.
		C3.1	1 (25.00)	- Morphine injection 3 mg prn q 8 hr was given but pain persisted (pain score of 10/10 points). Breakthrough pain also occurred.
P1.4	2 (4.88)	C1.1	1 (50.00)	- Pain persisted but analgesic drug was not prescribed.
		C6.4	1 (50.00)	- Breakthrough pain occurred, but morphine administration was not recorded by the nurse.

After discharge, there were 22 DRPs among 19 patients prescribed analgesic medications with an average of 1.16 DRPs per patient (Table 4). The most found DRP was P1.2 Effect of drug treatment not optimal (12 of 22 DRPs, or 55.45%) with the cause of C1.1 Inappropriate drug according to guideline/formulary. For example, patients had persistent pain but no morphine injection was prescribed for continuous pain control, and no prescription of morphine syrup for breakthrough pain. The second most DRP was P1.4 Untreated indication (6 of 22 DRPs, or 27.28%) with the cause of C1.1 Inappropriate drug according to guideline/formulary. For example, with a dyspnea score of 8/10, Berodual® nebulizer was prescribed during hospitalization but not for discharge. Other noticeable DRPs were P1.3 Unnecessary drug treatment, P1.1 No effect of drug treatment/therapy failure, and P3.2 Unclear problem/complaint.

Table 4 Drug related problems (DRPs) and associated causes after discharge according to PCNE v.7.0 (N = 22).

Problem code	No. (%)	Cause code	No. (%)	Example of DRP causes
P1.2	12 (54.55)	C1.1	12 (100.00)	- Morphine syrup was not prescribed for breakthrough pain. - Pain was persistent but morphine injection was not prescribed.
P1.4	7 (31.82)	C1.1	7 (100.00)	- No morphine injection or MST for continuous pain control was prescribed. - The patient denied hospitalization, and no analgesics were prescribed at discharge. - Patient had a dyspnea score of 8/10, but no morphine injection was prescribed. - With a dyspnea score of 8/10, Berodual® inhaler was prescribed during hospitalization but not at discharge.
P1.1	1 (4.55)	C7.8	1 (100.00)	- Patient was unable to receive morphine since no caregiver to administer the injection.
P1.3	1 (4.55)	C1.5	1 (100.00)	- MST, Morphine injection and morphine syrup were prescribed concomitantly.
P3.2	1 (4.55)	C3.2	1 (100.00)	- Dose of morphine syrup was 20% higher than usual around-the-clock dose, with no drug effect known.

Among patients who had **out-patient visits** after discharge, 13 DRPs were found with an average of 1.30 DRPs per patient. The most found DRP was P1.2 Effect of drug treatment not optimal (5 of 13 DRPs, or 38.46%) with e the cause of C1.1 Inappropriate drug according to guidelines/formulary. For example, no morphine syrup for breakthrough pain and C1.5 Inappropriate duplication of therapeutic group or active ingredient since pethidine injection was prescribed as the first choice instead of morphine injection. The second most DRP was P2.1 Adverse drug event occurring (3 of 13 DRPs, or 23.07%). For example, constipation with the cause of C1.8 Synergistic/preventive drug required and not given where laxative was not prescribed to prevent constipation caused by morphine. In addition, the DRP of P3.2 Unclear problem/complaint with the cause of

C5.2 Prescribing error, where administration method was not specified in the medical record by physician.

Among patients who were followed up by **home healthcare visits**, 7 DRPs were found with an average of 1.16 DRPs per patient. The most found DRP was P1.2 Effect of drug treatment not optimal (3 of 7 DRPs) with the cause of C1.1 Inappropriate drug according to guidelines/formulary (1 of 7 DRPs) where no alagesic medication was prescribed for breakthrough pain. The DRP of P2.1 Adverse drug event occurring was found where the symptom of nausea and vomiting cause by morphine MST was so severe that the patient could not take the drug. The DRP of P1.1 No effect of drug treatment/therapy failure was found with the cause of C7.5 Patient administers/uses the drug in a wrong way. This was because the patient's relative had crush or ground morphine MST so that the drug was ineffective to relieve the pain. Four DRPs in four patients were solved and recorded by investigating pharmacist providing home healthcare service by consultation with involving physicians and nurses. These DRPS included prescribing pattern adjustment such as changing dosage regimen to be suitable for administration and advising the patient to seek pain re-assessment at the hospital (Figure 1).

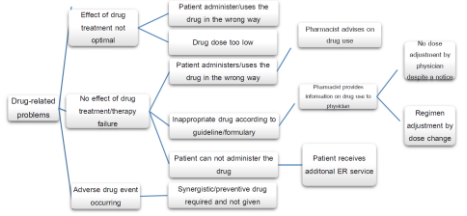

Figure 1 Drug related problems (DRPs) and associated causes found in home healthcare visits.

In terms of relationships between having DRP and various factors (age, gender, co-morbidity, hospitalization days, pain levels and palliative performance levels), there were no statistically significant relationships either during hospitalization or home healthcare visit except having DRP during hospitalization and pain levels (*P*-value = 0.046) (Table 5).

Table 5 Relationships between having drug related problems (DRPs) with various factors

	Variables	*P*-value*
Having DRP during hospitalization	Age (< 60 yrs, ≥ 60 yrs)	0.164
	Gender	0.127
	Co-morbidity (yes/no)	0.589
	Hospitalization days (≤ 5, > 6 days)	0.478
	Pain levels (0, 1–3, 4-6, 7-10 points)	0.046
	Palliative performance levels (0-30%, 40-60%, 70-100%)	0.197
Having DRP during home healthcare visit	Age (< 60 yrs, ≥ 60 yrs)	0.164
	Gender	0.486
	Co-morbidity (yes/no)	0.478
	Hospitalization days (≤ 5, > 6 days)	0.331
	Pain levels (0, 1–3, 4-6, 7-10 points)	0.526
	Palliative performance levels (0-30%, 40-60%, 70-100%)	0.197

* Chi-square test.

Discussions and Conclusion

Our study in end-stage cancer patients receiving palliative care found that most of the patients were male, and with severe pain and moderate level of palliative performance. More than 50% of the patients requiring opioid analgesics were given the drugs. Prescribing patterns were diverse among patients. Drug related problems (DRPs) during hospitalization were also diverse with those associated with drug selection as the most frequently found DRP. A given DRP could be associated with many causes. In addition, unclear problems were found left with no follow-up assessment. For example, with no follow-up assessment on pain level, effectiveness opioid analgesic was not known and further regimen adjustment could not be made.

In terms of opioid analgesic medications, morphine was prescribed more frequently than other opioid derivatives. This finding was consistent with the study of Erlenwein and colleagues[13] With various doses of morphine found in our study, 20 mg per day was the most prescribed dose during hospitalization. This dosage of morphine was similar to the one found in the study of Suecharoen and colleagues.[14] It has been known that opioid overdose could cause death. The dose of opioid derivative of more than 20 mg per day was associated with a higher risk of overdose-related death than the lower dose.[15] In our study, no sign of opioid overdose that could lead to death.

In terms of palliative performance level and the opioid analgesics, the study of Sathornviriyapong and co-workers found that the doses either higher or lower than 30 mg morphine-equivalent dose per day was not associated with death among patients with terminal cancer receiving palliative

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care.[16] This seems consistent with our study where different doses of opioid analgesics were not associated with the change of palliative performance. In other words, among patents followed up at the out-patient visit, their palliative performance decreased regardless of the morphine doses.

In terms of factors affecting morphine dose adjustment, a study with retrospective data review of Miura and colleagues (2014) found that dyspnea, age of less than years, and morphine dose of less than 50 mg per day were associated with the increase in morphine dose.[17] In our study, we tried to assess dyspnea but found that assessment of dyspnea was rarely performed and recorded. In the future, more dyspnea assessment could be highly useful for opioid derivative analgesic dose adjustment.

DRPs found in our study were relatively similar to a previous study[10], where the most found DRP was Effect of drug treatment not optimal with the cause of the absence of around-the-clock analgesic prescription. Other causes of this DRP included only symptomatic rescue medications prescribed which left the patient's pain poorly controlled and allowed breakthrough pain to occur despite having pain control medication. It was also found that the frequency of morphine administration was less than optimal. For example, morphine 3 mg iv q 6 hr was results in an inadequate pain control length since morphine offers 2 – 4 hours of pain suppression. In addition, dosage adjustment was suboptimal. Mostly frequency of administration, rather than dose adjustment according to pain level, was carried out. As a result, the dose of morphine was too low for the patient's pain level.

The most frequently found opioid related adverse effect during hospitalization was constipation. Constipation was a frequent and dose-independent effect of opioid derivatives. It is preventable with laxatives. However, in our study, among patients with constipation associated with opioid derivatives, laxative drugs were not given. However, in few patients, constipation persisted despite laxative use. These cases of persistent constipation could be due to the patient's physiological and behavioral factors. Since data of adverse effects were under recorded, the extent and severity of undesirable effects of opioid derivatives could be underestimated. The data of adverse effects of opioid analgesics were crucial for patient compliance to the drug. Patients could face nausea and vomiting symptom from morphine that is so severe that they could not continue the drug. This cause the DRP of No effect of drug treatment/ therapy failure. Therefore, a progressive follow-up to seek adequate information of opioid derivatives use and their adverse effects should be enforced and promoted. This information included but not limited to sedation score to assess opioid overdose. Other side effects of opioids to monitor were urinary retention, dry mouth, dry throat, nausea, and vomiting. Providing information regarding adverse effects of opioid derivatives could alleviate anxiety and enforce confidence associated with drug use among these patients.

Deviations of drug administration during hospitalization were found in our study. These deviations usually resulted in giving doses lower than prescribed. The finding could be useful for multidisciplinary team to improve the process together.

The absence of necessary prescriptions in some patients after discharge was a relatively substantial problem. With no necessary medications at home, disrupted care could be a result. In addition, drug dosage form inappropriate for given patients could bring about a problem. For example, some frail patients prescribed morphine injection may need a caregiver to administer the drug. With poor understanding, the caregiver could administer inappropriately and pain could not well controlled. To make the problems worse, the hospital lacked resources to help the patients administer the drug such as syringe driver. Poor analgesic administration could lead too poor control on pain and other physical distresses such as dyspnea.

From these findings, there is a room for improvement of the hospital to acquire materials and devices necessary for proper drug administration such as syringe driver for continuous infusion. Hospital formulary could be improved by adding analgesic dosage form more convenient self-care such as fentanyl transdermal patch for patients difficulty swallowing.

For patients followed up at the out-patient visits, a larger proportion of them were given around-the-clock opioid derivative analgesics than when hospitalized or discharged. DRPs at out-patient visits were similar to those during hospitalization and at discharge especially Effect of drug treatment not optimal, and unclear direction. The investigator had a discussion with the multidisciplinary team for further solutions.

For home healthcare visits, fewer patients were followed up by the procedure. This could be a result of unclear or nonspecific guideline on home visit. In addition, since these

patients were in their terminal stage of life, some of them passed away in a very short period of time that an urgent follow-up could not be made.

Among these home visits, like hospitalization and out-patient settings, the DRP of Effect of drug treatment not optimal was also found to be prominent. However, the causes of the problem were different from those settings and more factors were involved. For example, caregiver's misunderstanding on MST administration led to crushing or grinding the MST tablet. Home follow-up visit with pharmacist in the multidisciplinary team could help identify and solve DRPs in these patients with end-stage cancer. Previous studies revealed that multidisciplinary palliative care consultation team involving prescription and administration could help relieve DRPs.[11,16]

The assessment on pain level found in this study was inadequate since fewer patients were assessed for pain; some were assessed only during hospitalization. In addition, since specific types of pain were not thoroughly evaluated, medications suitable for specific causes of pain could not be prescribed. This was evident as adjuvant medications were prescribed in a very low portion of patients. Comprehensive pain control could not be achieved.

Like pain assessment, palliative performance level was also assessed in a small fraction of patients, mostly done during hospitalization. This inadequate assessment made adjustment on drug dosing and administration adjustment more difficult, if not impossible. For example, administration problem persisted in patients with swallowing problem who were given MST tablet.

In our study, having DRPs during hospitalization was significantly associated only with pain level, not gender, age, palliative performance level, or co-morbidity. A larger sample size could help shade clearer associations between having DRPs and various potential factors.

Our study has some limitations. Since the participants were in their terminal stage of life, not many of them could be available for a certain duration time for investigation. Representativeness of this small group of patients was somehow problematic, especially after discharge where fewer patients were able to attend out-patient and/or home healthcare visits. One should be cautious in interpretation on the later phase of follow-up. In addition, with the retrospective nature of study, some information in the medical records was incomplete or lost. Credibility of the results should be of caution. Furthermore, different evaluators on DRPs could yield different results. This was because the precision on identifying DRP was largely based on clinical experience of the evaluators. In the future, more prospective studies with reasonably long duration and larger sample size and better data collection method should be conducted. Such studies could offer clearer relationships between DRP and potential factors.

In conclusion, DRPs of opioid analgesics and related adjuvant medications among patient end-stage cancer receiving palliative care were found. Inconclusive assessment on pain and palliative performance made pain management in these patients suboptimal. The role of pharmacist in multidisciplinary team in palliative care should be encouraged.

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