

Assessment of Palliative Care Team Activities

—Survey of Medications Prescribed Immediately before and at the Beginning of Opioid Usage—

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We established the Terminal Care Study Group, consisting of physicians, pharmacists, and nurses, in September 2001, and developed the group into the Palliative Care Team. We have surveyed the state of concomitant medications immediately before and at the beginning of opioid usage (except injections) to assess the role of the Palliative Care Team. The survey period was 3 years from October 1, 2002 to September 30, 2005. While the frequency of the prescription of non-steroidal anti-inflammatory drugs (NSAIDs), laxatives, or antiemetics before the beginning of opioid administration did not differ significantly among the 3 periods, that at the beginning of opioid administration increased significantly in 2003 compared with 2002, and increased further in 2004. Many of the drugs used were those that were recommended in our cancer pain management program. Thus, the activities of the Palliative Care Team are considered to have led to proper measures for the control of the major adverse effects of opioids such as constipation and nausea/vomiting in addition to pain control in accordance with the WHO's pain ladder, and also contributed to improvements of the patients' QOL.

Key words—palliative care team; pain; opioid; non-steroidal anti-inflammatory drug; laxative; antiemetic

INTRODUCTION

In 1986, the World Health Organization (WHO) compiled "Cancer Pain Relief", a guideline for the control of cancer pain in which morphine administration plays a central role.¹⁾ This has prompted renewed understanding of the usefulness of morphine as an analgesic, and cancer pain management has since developed rapidly worldwide. Opioid consumption has also increased. Recently, many opioid preparations in various compositions and dosage forms have been approved, and proper knowledge of them has become necessary for their appropriate use. We, therefore, established the Terminal Care Study Group, consisting of physicians, pharmacists, and nurses, in September 2001, and developed the group into the Palliative Care Team. The team has conducted educational activities concerning the use of pain remedies and analgesic adjuvants and measures to control the adverse effects of opioids based on the WHO method. We have surveyed the state of concomitant medications

immediately before and at the beginning of opioid usage (except injections) to assess the role of the Palliative Care Team.

MATERIALS AND METHODS

History of Activities of the Palliative Care Team and Role of Pharmacists Municipal Ikeda Hospital (our hospital) is a medium sized public hospital for acute diseases with 364 beds. Since it has no palliative care ward, terminal cancer patients are also admitted to the general ward and given terminal care.

Table 1 shows the history of the Palliative Care Team. It was started in September 2001 as the Terminal Care Study Group, with the participation of physicians, pharmacists, and nurses. The members of the Study Group were approved as a Palliative Care Team by the hospital in June, 2002, when the cancer pain treatment program of the hospital (1st edition, A4 size; 2nd edition, A6 size) was prepared. The first edition was distributed only to departments and ward stations, but the second edition was distributed to all physicians, pharmacists, and nurses.

Three pharmacists were appointed as members of

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Table 1. History of the Palliative Care Team in Municipal Ikeda Hospital

September, 2001	Establishment of the Terminal Care Study Group (consisting of interested physicians, nurses, and pharmacists)
February, 2002	Issuing of the first edition of the Municipal Ikeda Hospital Pain Program and the beginning of palliative care using the pain chart
April, 2002	Employment of Oncology-Certified Nurse Specialists
April, 2003	Appointment of link nurses on each ward. Participation of surgeons.
April, 2004	Approved as a team within the hospital (Municipal Ikeda Hospital Palliative Care Team)
June, 2004	The second edition of the Municipal Ikeda Hospital Cancer Pain Program was issued
July, 2004	Participation of anesthesiologists

the Palliative Care Team while they remained as pharmacy members. The primary role of the pharmacists in the Palliative Care Team was the preparation of a cancer pain management program. This cancer pain management program describes methods for the use of pain remedies and analgesic adjuvants primarily for cancer pain management based on the WHO method and measures to control their adverse effects (Table 2). This program was authored and edited primarily by pharmacists. The pharmacists also participated in weekly cancer conferences and ward rounds of the Palliative Care Team. At the case conferences and ward rounds, the pharmacists designed prescriptions and made proposals on the basis of the cancer pain management program. Furthermore, they provided guidance in drug management to individual patients needing palliative care and information concerning drug therapy with palliative medicine to the hospital staff.

Survey of Concomitant Medications Prescribed Immediately before and at the Beginning of Opioid Usage The survey period was 3 years from October 1, 2002 to September 30, 2005. The 3 years were divided into three 1-year periods, *i.e.*, October 1, 2002–September 30, 2003 (year 2002), October 1, 2003–September 30, 2004 (year 2003), and October 1, 2004–September 30, 2005 (year 2004), and drugs that were prescribed immediately before the beginning, and simultaneously with, the first use of an

Table 2. Contents of the Cancer Pain Treatment Program of Municipal Ikeda Hospital

I. Classification of cancer pain [Anesthetist]
1. Somatic pain
2. Visceral pain
3. Neuropathic pain
II. WHO Cancer Pain Relief Guidelines [Pharmacist]
1. Step 1 (NSAIDs)
2. Step 2 (NSAIDs+Opioid for mild to moderate pain)
3. Step 3 (NSAIDs+Opioid for moderate to severe pain)
4. If pain cannot be controlled, or oral administration is impossible, in the third stage.
III. Countermeasure against adverse effects of opioids [Pharmacist]
IV. Analgesic adjuvant [Pharmacist]
1. Neuropathic pain
2. Pain of compression neuropathies
3. Pain of bone metastasis
V. Classification of nerve block [Anesthetist]
1. Epidural block
2. Intrathecal phenol block
3. Celiac plexus block (Splanchnic nerve block), Inferior mesenteric plexus block, Superior hypogastric plexus block
VI. Method of requesting consultant to Palliative Care Team [Nurse]

[]: Author of chapter

opioid in each patient were investigated. The drugs of interest were non-steroidal anti-inflammatory drugs (NSAIDs), laxatives, and antiemetics. Prescription data were obtained from the order entry system and sorted concerning each opioid preparation. However, patients in whom opioid injections were used were excluded. Statistical analyses of the data were performed by the Chi-square and Kruskal-Wallis tests using SPSS.

RESULTS

Characteristics of Patients Using Opioids No significant difference was observed in the male-female ratio, mean age, or department among the 3 periods (Table 2). As for the components of opioid preparations, the percentage of morphine decreased, oxycodone serially increased, and fentanyl also increased slightly (Table 3).

Comparison of Concomitant Medications Prescribed Immediately before and at the Beginning of Opioid Usage

(1) **Frequency of the Use of NSAIDs and Preparations Used** NSAIDs were prescribed immediate-

Table 3. Characteristics of the Study Patients

	2002.10.1–2003.9.30 (n=82)	2003.10.1–2004.9.30 (n=83)	2004.10.1–2005.9.30 (n=106)	p value
Sex (male : female)	38 : 44	47 : 36	65 : 41	<i>p</i> =0.118 ^{a)}
Mean age (y)	66.9±11.9	68.4±11.2	65.5±13.6	<i>p</i> =0.401 ^{b)}
Diagnosis and treatment department				
internal medicine	35	47	62	} <i>p</i> =0.208 ^{a)}
surgery	24	23	25	
gynecology	11	3	8	
urology	7	8	7	
dermatology	2	0	1	
orthopedics	0	1	0	
ophthalmology	0	1	0	
otolaryngology	0	0	1	
neurology	0	0	1	
dentistry	3	0	1	

a) Chi-square test, b) Kruskal-Wallis test

ly before the use of opioids in slightly less than 80% of the patients in all 3 periods, with no significant difference. However, the percentage of patients prescribed NSAIDs simultaneously with opioids was 34.2% in 2002 but increased to 65.0% in 2003 and 77.3% in 2004 (Fig. 1). Of the NSAIDs used immediately before the beginning of opioid usage, loxoprofen sodium tablets accounted for about 50% in all 3 periods. However, the NSAID most frequently prescribed simultaneously with opioids was loxoprofen sodium tablets, accounting for 47.4%, in 2002, but etodolac tablets, accounting for 45.8%, in 2004 (Table 4).

(2) Frequency of the Use of Laxatives and Preparations Used Laxatives were used immediately before opioid usage in 20–40% of the patients in all 3 periods. However, they were used simultaneously with opioids in 48.7% in 2002 but in 71.1% in 2003, showing a significant increase, and in 76.4% in 2004, showing a slight increase (Fig. 2). The laxative most frequently used was magnesium oxide powder, both immediately before and after the beginning of opioid usage (Table 4).

(3) Frequency of the Use of Antiemetics and Preparations Used Antiemetics were prescribed immediately before the beginning of opioid usage in 30–60% of the patients in all 3 periods. However, they were prescribed simultaneously with opioids in 46.3% of the patients in 2002 but in 72.3% in 2003, showing a significant increase, and in 73.6% in 2004, showing a slight increase (Fig. 3). The antiemetic

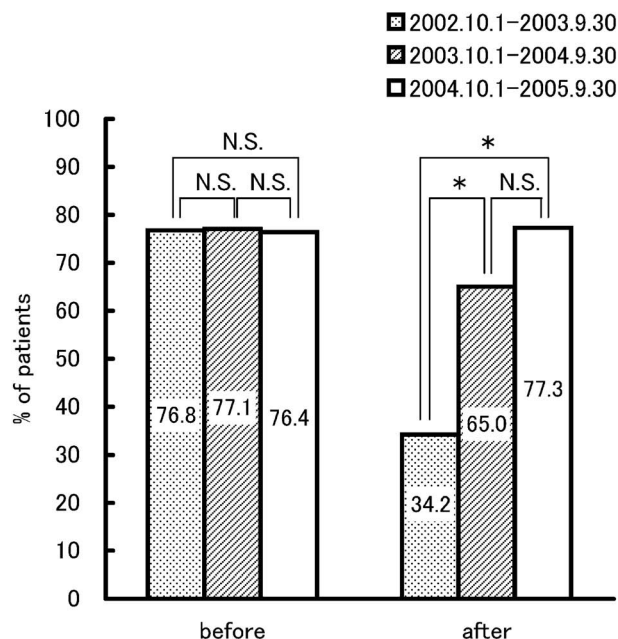


Fig. 1. Percentage of Patients Prescribed Non-steroidal Anti-inflammatory Drugs (NSAIDs) before and after the Beginning of Opioid Usage.

The survey period was 3 years from October 1, 2002 to September 30, 2005. The 3 years were divided into three 1-year periods. before: immediately before the beginning of opioid usage. after: at the beginning of opioid usage. **p*<0.01 by Chi-square test. N.S.: not significant.

most frequently prescribed with opioids was prochlorperazine maleate tablets (Table 4).

DISCUSSION

Opioids are primary drugs in cancer pain treatment according to the WHO method, and their amount of

Table 4. Number of Patients Using Opioids

	2002.10.1–2003.9.30 (n=82)	2003.10.1–2004.9.30 (n=83)	2004.10.1–2005.9.30 (n=106)	p value
Modified-release morphine sulfate (or Rapid-release morphine hydrochloride)	77	42	43	} p<0.001
Modified-release Oxycodone hydrochloride	2	36	54	
Fentanyl patch	3	5	9	

Chi-square test

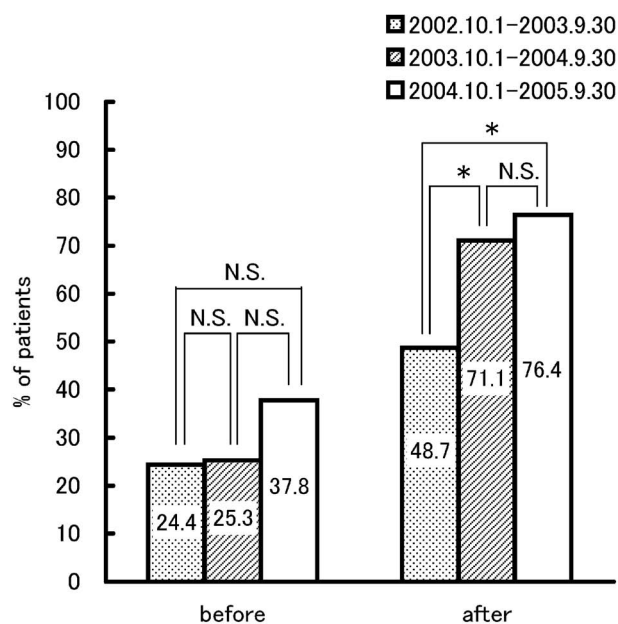


Fig. 2. Percentage of Patients Prescribed Laxatives before and after the Beginning of Opioid Usage.

The survey period was 3 years from October 1, 2002 to September 30, 2005. The 3 years were divided into three 1-year periods. before: immediately before the beginning of opioid usage. after: at the beginning of opioid usage. * $p<0.01$ by Chi-square test. N.S.: not significant.

usage is increasing annually in Japan as well as in other advanced countries.²⁾ Therefore, opioids and associated remedies must be used properly. We, thus, established the Terminal Care Study Group, consisting of physicians, pharmacists, and nurses, in September 2001 and performed educational activities concerning the use of pain remedies and adjuvant analgesics based on the “WHO method” and measures to control the adverse effects of opioids. As a result, the frequency of rescue prescriptions was about 10% until 2001, but was reported to have increased to 71.4% in 2003.³⁾ In this study, to assess the roles of pharmacists in the activities of the Palliative Care Team, we evaluated the drugs prescribed immediately before and at the beginning of opioid usage

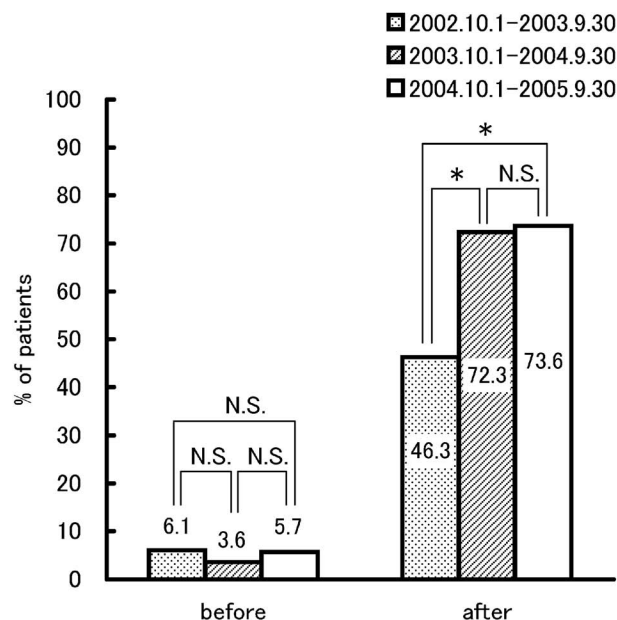


Fig. 3. Percentage of Patients Prescribed Antiemetics before and after the Beginning of Opioid Usage.

The survey period was 3 years from October 1, 2002 to September 30, 2005. The 3 years were divided into three 1-year periods. before: immediately before the beginning of opioid usage. after: at the beginning of opioid usage. * $p<0.01$ by Chi-square test. N.S.: not significant.

(other than injections) concerning NSAIDs, which are pain remedies based on the “WHO method”, and laxatives and antiemetics, which are used for the prevention of major adverse effects of opioids, *i.e.*, constipation and nausea/vomiting.

By the “WHO method”, NSAIDs are used in the first stage of cancer pain treatment. Also, if no sufficient effect is obtained even by increasing the dose of NSAIDs, opioids are used. However, the use of NSAIDs should be continued with opioids unless there is a contraindication to them. The cancer pain treatment program of our hospital has recommended the concomitant use of etodolac tablets with a highly selective COX-2 inhibitor activity even after the beginning of opioid usage.

Table 5. Percentages of Patients Administered Various Preparations out of Those Prescribed Non-steroidal Anti-inflammatory Drugs (NSAIDs), Laxatives, and Antiemetics

		2002.10.1–2003.9.30		2003.10.1–2004.9.30		2004.10.1–2005.9.30	
		before	after	before	after	before	after
NSAIDs	Etodolac tablet	4.3	15.8	28.1	40.4	27.9	45.8
	Loxoprofen sodium tablet	54.3	47.4	50.9	44.7	54.1	36.1
	Diclofenac sodium tablet	15.2	5.3	1.8	2.1	1.6	0.0
	Diclofenac sodium SR capsule	4.3	10.5	10.5	10.6	6.6	4.2
	Ampiroxicam capsule	2.2	0.0	0.0	0.0	0.0	0.0
	Lornoxicam tablet	4.3	10.5	1.8	0.0	3.3	1.4
	Zaltoprofen tablet	2.2	0.0	3.5	0.0	3.3	0.0
	Aspirin powder	0.0	0.0	1.8	2.1	0.0	0.0
	Tiaramide hydrochloride tablet	0.0	0.0	0.0	0.0	1.6	0.0
	Diclofenac sodium suppository	23.9	15.8	5.3	0.0	4.9	8.3
	Indometacin suppository	2.2	0.0	0.0	0.0	0.0	0.0
Flurubiprofen axetil injection	0.0	0.0	0.0	0.0	0.0	4.2	
Laxatives	Magnesium oxide powder	60.0	81.8	85.7	86.2	70.6	91.0
	Senoside tablet	30.0	18.2	4.8	5.2	20.6	7.7
	Senna powder	5.0	3.0	0.0	0.0	0.0	0.0
	Sodium picosulfate liquid	0.0	3.0	9.5	10.3	23.5	19.2
	New Lecicarbon® suppository	5.0	0.0	0.0	0.0	0.0	0.0
Antiemetics	Prochlorperazine maleate tablet	0.0	83.8	66.7	98.3	100.0	89.5
	Metoclopramide tablet	75.0	10.8	33.3	3.3	25.0	2.6
	Domperidone tablet	25.0	10.8	0.0	0.0	0.0	5.3
	Haloperidol tablet	0.0	0.0	0.0	1.7	0.0	0.0
	Domperidone suppository	25.0	2.7	0.0	0.0	0.0	0.0
	Metoclopramide injection	0.0	0.0	0.0	0.0	0.0	2.6

* before: immediately before the beginning of opioid usage, after: at the beginning of opioid usage

Cancer pain treatment by the “WHO method” requires strict implementation of preventive measures against the adverse effects of analgesics. Concerning the relationship between the plasma opioid concentration and Pharmacological activities, constipating, emetic and analgesic effects generally appear first with an increasing plasma opioid concentration.⁴⁾ Constipation has been reported to occur in 82% of patients using morphine,⁴⁾ and as resistance to constipation is unlikely to develop, the concomitant administration of preventive laxatives is necessary in patients using morphine. Also, nausea has been reported to appear in 40–70% of terminal patients, and its control is another important problem.^{5,6)} Particularly, nausea is considered to occur in about a third of patients ad-

ministered opioids.^{6,7)} From these observations, administration of antiemetics is preferable.⁸⁾ There is no special laxative for the treatment of constipation due to opioids.⁹⁾ Primarily, stimulant or osmotic laxatives are used. Magnesium oxide powder, an osmotic laxative, is used frequently as a basic prescription despite its relatively weak effect.¹⁰⁾ Thus, the cancer pain management program of our hospital recommends the concomitant use of magnesium oxide powder with opioids for the prevention of constipation. If the laxative effect of magnesium oxide powder is insufficient, the program recommends the administration of stimulant laxatives. It also recommends the administration of prochlorperazine maleate tablets for the prevention of nausea.

According to the present survey, while the frequency of the prescription of NSAIDs, laxatives, or antiemetics before the beginning of opioid administration did not differ significantly among the 3 periods, that at the beginning of opioid administration increased significantly in 2003 compared with 2002, and increased further in 2004. Many of the drugs used were those that were recommended in our cancer pain management program. These were the results of the case conferences, proposal of the cancer pain management program following the “WHO method,” and guidance and educational activities based on the program that we have conducted since the establishment of the Terminal Care Study Group in September 2001. Also, the frequency of the prescription of the above drugs increased markedly in 2003 and 2004, probably because of the distribution of the A6-size (pocket-size) second edition of the Cancer Pain Management Program to all physicians, pharmacists, and nurses. These results were in parallel with the previously reported changes in the frequency of rescue prescriptions.³⁾

Recently, pharmacists have become actively involved in Palliative Care Teams at many general hospitals without a hospice ward.¹¹⁻¹³⁾ Maruyama, *et al.* reported that pharmacists’ constructive advice to physicians contributes to the safe and appropriate administration of opioids to cancer patients and improvements in their QOL.¹³⁾ Kataoka, *et al.* also reported that activities of the Palliative Care Team led to appropriate prescriptions of rescue doses.¹⁴⁾ At our hospital, also, the active involvement of pharmacists in the Palliative Care Team has promoted appropriate prescriptions of NSAIDs, laxatives, and anti-emetics based on the WHO pain ladder. Thus, the active involvement of pharmacists in the Palliative Care Team is very important for improving the patients’ QOL. With the approval of even more opioid preparations expected in the future, the importance of team care will increase further.

REFERENCES

- 1) World Health Organization, “Cancer Pain Relief,” ed. by World Health Organization, Geneva, 1986.
- 2) Yamanouchi T., Nagata Y., Kawashiri N., Mimura Y., Kawakami J., Adachi I., *J. Pharm. Soc. Jpn.*, **124**, 13–18 (2004).
- 3) Myotoku M., Murayama Y., Nakanishi A., Kawaguchi S., *Jpn. J. Pharm Health Care Sci.*, **31**, 1012–1018 (2005).
- 4) Koido K., Saito K., Sawada D., Hayasaka K., Miyano S., Yoshino K., “Morphine ni yoru Gan-totsu Kanwa,” ed. by Department of Pharmacy, National Cancer Center Hospital, MIX/Elsevier Science K. K., Tokyo, 2001, pp. 108–170.
- 5) Mannix K.A., “Palliation of Nausea and Vomiting,” Oxford Textbook of Palliative Medicine, 3rd, Oxford University Press, Oxford, 2004, pp. 333–334, 459–468.
- 6) Tuneto S., “New Palliative Medicine,” Saishin-igaku Corp., Osaka, 1999, pp.93–102.
- 7) McNicol E., Horowicz-Mehler N., Fisk R.A., Bennett K., Gialeli-Goudas M., Chew P.W., Lau J., Carr D., *J. Pain*, **4**, 231–256 (2003).
- 8) Twycross R., “Oral Morphine, Pain Relief in Advanced Cancer,” Churchill Livingstone, London, 1994, pp. 307–332.
- 9) Ikenaga M., *Clinics & Drug Therapy*, **15**, 253–255 (1996).
- 10) Gomyo I., “Gan shumatuki · Nanchisei sinkei-kin sikkankin sinko-ki no syozyo control,” eds. by Gomyo I., Hiratsuka R., Sato K., Kyo S., Nanzando Co., Ltd., Tokyo, 2000, pp. 84–93.
- 11) Sekine H., Yada M., *Yakkyoku*, **53**, 1523–1530 (2002).
- 12) Mantani M., Inoue Y., Nakajima N., Isikawa M., *Pharmaceuticals Monthly*, **47**, 247–252 (2005).
- 13) Maruyama M., Arakawa Y., Okada H., Eguchi T., Katou T., Ishikawa D., Iizuka A., Honda I., *Jpn. J. Pharm. Health Care Sci.*, **32**, 1222–1227 (2006).
- 14) Kataoka T., Wakamiya N., Sato T., Shino M., Takahashi A., Adachi I., *Jpn. J. Pharm. Health Care Sci.*, **32**, 1248–1253 (2006).