【招待講演 1】15:40-16:40　座長　並木昭義（札幌医科大学）

オピオイドローテーションの臨床的意義

樽見葉子
Physician Consultant, Regional Palliative
Care Program, Grey Nuns Community Hospital

Clinical implication of opioid rotation

Yoko Tarumi, Regional Palliative Care Program, Grey Nuns Community Hospital 172-177

【招待講演２】　9:20-10:20　座長　花岡一雄（東京大学）

Expectations of Peripheral Opioid Analgesia

J.G. Collins
Department of Anesthesiology, Yale University School of Medicine 179-180

【ランチョンセミナー２】 11:40-13:00　座長　土肥修司（岐阜大学）

ランチョンセミナー／昼食

在宅ホスピス・緩和ケアにおける疼痛緩和の実際と問題点

川越　厚（グループ・バリアン代表、ホームケアクリニック川越院長）

Management of cancer pain in outpatients

Atsushi Kawagoe
Home Care Clinic Kawagoe 178

Clinical Implication of Opioid Rotation

Author: Yoko Tarumi, M.D., Regional Palliative Care Program, Edmonton, Alberta

A. Introduction

Pain relief and palliative care have been the focus of increasing attention both in Japan and internationally. In Japan, cancer has been the leading cause of death since 1981. Three hundred thousand of people died from cancer in 2000 (1). Although the consumption of morphine has been significantly increasing in Japan, the average daily consumption of opioid is still considerably lower than in North America, Australia, Great Britain and western European countries (2). A 1996 survey (3) reflected generally poorer cancer pain control in Japanese university hospitals and cancer centers compared to previous studies of the WHO analgesic ladder.

One factor that may be contributing to poorer pain control is the limited selection of opioids for cancer pain relief compared with many other developed nations. Morphine, codeine and fentanyl transdermal therapeutic system are currently the only available opioid agonists for the management of moderate to severe cancer pain in Japan. In contrast, hydromorphone, oxycodone and methadone are available in addition to these three opioids in North America. Social and regulatory barriers may pose significant obstacles to access, even for clinicians experienced with the use of these agents.

B. What is Opioid Rotation?

Opioid rotation (also known as opioid substitution) is the practice of switching from one opioid to another, in order to improve an unfavourable balance of analgesia and side effects. Opioids are generally the most effective treatment for patients with cancer pain (4), and pain can be effectively controlled in most cancer patients with minimal toxicity until their last time. Morphine appears to have no clinically relevant ceiling effect to analgesia. Clinical reports of morphine dosed at 35-40 g/day emphasize this fact (5)(6). A point may be reached at which higher doses could theoretically produce greater analgesia but dose escalation is not possible because adverse effects supervene, thus effectively defining the responsiveness of the pain syndrome in that particular patient (5). Adverse effects of opioids are generally classified into two groups: (A) those usually seen with lower doses or in the early phase of opioid therapy, such as ventilatory depression, nausea and constipation; (B) those that may occur with chronic opioid therapy and are thought to be manifestations of central nervous systems hyperexcitability, such as allodynia, hyperalgesia, myoclonus, hallucinations, and delirium (i.e. opioid neurotoxicity). Patients with predictors for intractable pain such as neuropathic pain, incident pain, history of alcoholism or drug abuse, expression of psychosocial distress as somatic symptoms, and rapid development of tolerance, may experience opioid dose escalation and be at higher risk of opioid neurotoxicity (7).

The rationale for opioid rotation is based on inter-individual variability in response to different opioids, or intra-individual variability in response to the same opioid over time, which are commonly appreciated clinical phenomena in the management of cancer pain. There have been various hypotheses to explain these observations:

B-1-1. Genetic factors Genetic factors may be important in determining patterns of opioid

sensitivity. For example, some mouse strains are deficient in their expression of mu receptors (8), and are correspondingly insensitive to the analgesic effects of morphine (9). Sensitivity to mu and kappa analgesia has been demonstrated to vary independently across mouse strains, suggesting that each receptor subtype is under independent genetic control (10). It may be postulated, therefore, that analgesic and non-analgesic response to an opioid in humans may depend on a genetically determined pattern of expression of receptor subtypes for which that opioid is selective.

B-1-2. Opioid tolerance and incomplete cross-tolerance Individual variability in response to opioids has been postulated to reflect the development of tolerance and the existence of incomplete cross-tolerance between opioids (11). Analgesic tolerance is a phenomenon in which exposure to the opioid itself causes the patient who has achieved analgesia to require a higher dosage to maintain the same level of effect (12). Tolerance may also develop to adverse effects of opioids. Various mechanisms are thought to underlie incomplete cross-tolerance between opioids. In vivo studies comparing mu and kappa agonists suggest that the limited cross-tolerance results in part from the presence of multiple opioid receptor subtypes (13). Incomplete cross-tolerance among mu-opioid agonists may result from differences in the intrinsic efficacy (14). If tolerance for analgesia develops more rapidly than for adverse effects from opioids, this could manifest clinically as an imbalance in analgesic and adverse effects. Switching opioids could restore a favourable balance if cross-tolerance was incomplete, and if cross-tolerance for analgesia was less than that for adverse effects.

B-1-3. Opioid metabolites Morphine undergoes glucuronide conjugation and become two major metabolites: morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) (15). In animal models, M6G is 10- to more than 100-fold more potent an antinociceptive agent than morphine, and is longer acting when given in equi-effective doses (16).

M-3-G has no intrinsic analgesic action, consistent with its poor affinity for classical inhibitory opioid receptors in vitro (17). Following intracerebroventricular (ICV) and intrathecal administration, M-3-G evokes dose-dependent excitatory behavioral effects in rodents, and has a 10-fold higher excitatory potency than morphine (18)(19). ICV M-3-G can attenuate morphine- or M-6-G-induced antinociception and ventilatory depression (20). Although the effects of M-3-G in humans have not been well documented, patients who developed myoclonus, confusion or seizures on morphine in the setting of renal failure were found to have high plasma and cerebrospinal fluid (CSF) levels of M-3-G (21)(22).

Clinically, the plasma and CSF concentrations of M-3-G exceed those of morphine by several-fold after single doses of morphine (23), and by as much as 10- to 20-fold in patients receiving morphine chronically (24). A systematic review showed that metabolite ratios of M-6-G and M-3-G to morphine were higher in renal impairment, and routes of administration which avoided first pass metabolism (intravenous, transdermal, rectal, intramuscular, epidural and intrathecal) resulted in lower metabolite production than oral, sublingual, or buccal (25). Opioid rotation may possibly benefit patients with opioid hyperexcitability by allowing clearance of the offending metabolites. Theoretically, opioids without known active metabolites, such as methadone, may be associated with a lower incidence of opioid-induced hyperexcitablity (26).

Numerous case reports and small retrospective case series have suggested improvement in the balance of opioid analgesia and adverse effects in cancer patients after opioid rotation. Three large retrospective studies have supported these observations (27)(28)(29). Three small prospective uncontrolled studies (30)(31)(32) have also yielded positive findings.

B-2. Other indications for opioid rotation

Other issues of a clinical, practical or economic nature may influence a decision to switch opioids. Fentanyl transdermal therapeutic system is a favourable option for patients who have stable pain but difficulty with oral intake due to disorders of the gastrointestinal tract or dysphagia secondary to neurological disease. However, due to the prolonged time to achieve steady-state blood levels 33), this delivery system is not suitable for situations in which rapid dose titration is required (e.g. acute uncontrolled pain or incident pain without an appropriate breakthrough analgesic regimen). Methadone's unique properties include lack of known active metabolites (34), possible antagonism of the N-methyl-D-aspartate receptor (35), incomplete cross-tolerance with other opioids (36) and a logarithmic increase in relative potency at higher doses (37). It is also the least expensive opioid. Methadone may therefore be advantageous in the settings of renal failure, neuropathic pain, opioid tolerance and requirement for high opioid doses. Cost-effectiveness may be a crucial issue for Japanese palliative care units, for which the cost of care is already fixed, as well as for the Japanese medical system in general, which is carrying a huge debt.

C. Clinical Implications

When confronted with a patient with an unsatisfactory response to opioid therapy, a careful multidimensional assessment of the underlying pain is essential. A multidimensional assessment takes into account not only characteristics of the pain and opioid response, but also factors that may influence the perception and expression of pain. It is important to remember that pain expression does not necessarily correlate with nociception. Two patients with the same etiology of pain causing similar nociception may perceive and express pain in a completely different manner. Assessment of pain without a multidimensional approach ignores the complexity of the pain experience.

Two tools may assist the multidimensional assessment of pain. The Edmonton Symptom Assessment System (ESAS)(38) measures nine symptoms using visual analogue scales: pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. The ESAS is completed by the patient, if possible. It places pain in the context of other symptoms, assesses outcomes of interventions and can be used to track individual patients over time. The Edmonton Staging System (38) is a tool for identifying predictors of intractable pain such as neuropathic pain, incident pain, impaired cognitive functioning, major psychological distress, opioid tolerance and history of drug or alcohol abuse. These assessment tools are particularly useful to draw attention to patients who express their psychological, social or spiritual distress as physical pain (somatization). Those patients are at risk of escalating their doses of opioids, resulting in toxicity with little or no pain relief. This type of pain may improve with counseling, socialization, physical activity, or other distraction.

However, it is not sure if these assessment tools are applicable internationally since the expression of pain as well as mood (anxiety/depression) may vary depending on patients' cultural or religious backgrounds (39).

Opioid hyperexcitability is often associated with delirium and probably does not have a single common etiology. It is therefore important to consider correctable factors contributing to delirium. The etiology of delirium other than opioids may be follows: primary or metastatic intracranial disease, metabolic encephalopathy, electrolyte imbalance, chemotherapy, steroids, radiation, anticholinergics, antiemetics, antivirals, infection, nutritional deficiencies, paraneoplastic

syndromes, etc. Theoretically, it is reasonable to treat these possible-contributing factors to delirium while observing the patient's progress without switching the opioid. However there is an ethical concern for potentially delaying definitive treatment in fragile advanced cancer patients with limited life expectancy. Clinically, it is more beneficial for these patients to clear all the possible aggravating factors in delirium and hyperexcitablity, particularly when the symptoms are severe.

Several strategies have been recommended to manage opioid-related hyperexcitability. These include switching from one opioid to another, hydration, and reducing the opioid dose. Reducing the opioid dose is only indicated when pain is well controlled in the presence of mild opioid-related hyperexcitability. Hydration is advocated on the grounds that it promotes the renal elimination of opioid metabolites. A combination of rotating to an alternative opioid and hydration is often effective. The choice of opioid is, at the moment, empirical. While there may be theoretical grounds to switch to an opioid with particular pharmacological properties, the relationship between experimental findings and clinical experience has not yet been established.

When considering opioid rotation, potency and equianalgesia are two important concepts of opioid pharmacodynamics that require attention. Potency refers to the power of a medicinal agent to generate its desired outcome that is the dose required to produce a given effect. A more potent agent becomes beneficial when a limited volume is an issue, such as in subcutaneous infusions (40). Equianalgesia refers to different doses of two agents that provide approximate pain relief (40)(41).

Several equianalgesic dose tables are generally used to aid the clinician in converting from one opioid to another. It has to be emphasized that much of the information in these tables has been derived from single-dose studies that are more appropriate for the management of acute pain. Only a limited number of studies have assessed opioid equianalgesic dose ratios in the context of chronic pain management (41).

The bioavailability of each opioid, inter-individual or inter-racial genetic variability in the metabolism of each opioid, or incomplete cross-tolerance between opioids may play significantly influence the equianalgesic dose ratio. It is therefore crucial to monitor clinically until stable pain control and opioid doses have been achieved.

E. Conclusion

Opioid rotation has become a generally accepted practice for cancer pain relief internationally. It is important to be aware of complexity of the pain experience and perform a multidimensional assessment. Identifying potentially intractable pain and intervening in their earlier stage may lead to successful pain relief. When opioid rotation is considered, excluding other contributing factors for opioid neurotoxicity, and using appropriate equianalgesic dose ratios with careful and close monitoring of patients' pain and other symptoms are extremely important.

References

(1) Annual mortality trends by leading causes of death in Japan (1930-1998). Cancer statistics in Japan in 1999. Foundation for Promotion of Cancer Research.
(2) Achieving Balance in National Opioid Control Policy: Guidelines for assessment. World Health Organization, 2000. http://www.medsch.wisc.edu/painpolicy/publicat/00whoabi/00whoabi.htm.
(3) Hiraga K, Takeda F. Current situation and prospect in the management of cancer pain in Japan. Palliative Care Medicine (Japanese) 1999; 1:134-42.

(4) Zech DFJ, Grond S, Lynch J,Hertel D, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief. A 10-year prospective study. Pain 1995; 63: 65-7.
(5) Portenoy RK, Moulin DE, Rogers A, Inturrisi CE, Foley KM. IV infusion of opioids for cancer pain: clinical review and guidelines for use. Cancer Treat Rep 1986; 70:575-81
(6) Donahue SR. Morphine sulfate intravenous dose of 1650 mg per hour. Hosp Pharm 1989; 24:311.
(7) Bruera E, Schoeller T, Wenk R, MacEachern T, Marcelino S, Suarez-Almazor M, Hanson J. A prospective multi-center assessment of Edmonton Staging System for cancer pain. J Pain Symptom Manage 1995; 10:348-55.
(8) Moskowitz AS, Goodman RR. Autoradiographic analysis of Mu1, Mu2, and delta opioid binding in the central nervous system of C57BL/6BY and CXBK(opioid receptor-deficient) mice. Brain Res 1985; 360:118-116.
(9) Vaught JL, Mathiasen JR, Raffa RB. Examination of the involvement of supraspinal and spinal mu and delta opioid receptors in analgesia using the mu receptor deficient CXBT mouse. J Pharmacol Exp Ther 1988; 245:13-16.
(10) Pick CG, Cheng J, Paul D, Pasternak GW. Genetic influences in opioid analgesic sensitivity in mice. Brain Res 1991; 566:295;298.
(11) Watanabe S. Intraindividual variability in opioid response: a role for sequential opioid trials in patient care. In: Portenoy RK, Bruera E, eds. Topics in Palliative Care; vol. 1. New York: Oxford University Press; 1997:195-203.
(12) Portenoy RK, Savage SR. Clinical realities and economic considerations: special therapeutic issues in intrathecal therapy—tolerance and addiction. J Pain Symptom Manage 1997; 14:27-35.
(13) Moulin DE, Ling GSF, Pasternak GW. Unidirectional analgesic cross-tolerance between morphine and levorphanol in the rat. Pain 1988; 33:233-239.
(14) Stevens GW, Yaksh TL. Time course characteristics of tolerance to continuously infused antinociceptive agents in rat spinal cord. J Pharmacol EXP Ther 1989; 251:216-223.
(15) Milne RW, Nation RL, Somogyi AA. The disposition of morphine and its 3- and 6-glucuronide metabolites in humans and animals, and importance of the metabolites to the pharmacological effects of morphine. Drug Metab Rev 1996; 28:345-472.
(16) Stain F, Barjavel MJ, Sandouk P, Plotkine M, Scherrmann JM, Bhargava HN. Analgesic response and plasma and brain extracellular fluid pharmacokinetics of morphine and morphine-6beta-d-glucuronide in the rat. J Pharmacol Exp Ther 1995; 274:852-7.
(17) Loser SV, Meyer J, Freudenthaler S, Sattler M, Desel C, Meineke I, Gundert-Remy U. Morphine-6-O-beta-D-glucuronide but not morphine-3-O-beta-D-glucuronide binds to mu-, delta-, and kappa-specific opioid binding sites in cerebral membranes Arch Pharmacol 1996; 354:192-7.
(18) Yaksh TL, Harty GJ, Onofrio BM. High doses of spinal morphine produce a non-opiate receptor-mediated hyperesthesia: clinical and theoretic implications. Anesthesiology 1986; 64:590-7.
(19) Bartlett SE, Cramond T, Smith MT. The excitatory effects of morphine-3-glucuronide are attenuated by LY274614, a competitive NMDA receptor antagonist, and by midazolam, an agonist at the benzodiazepine site on the GABAA receptor complex. Life Sci 1994; 54:687-94.
(20) Gong QL, Hender J, Bjorkman R, Hender T. Morphine-3-glucuronide may functionally anatagonise morphine-6-glucuronide induced antinociception and ventilatory depression in the rat. Pain 1992; 48:249-55.
(21) Sjogren P, Dragsted L, Christensen CB. Myoclonic spasms during treatment with high doses of intravenous morphine in renal failure. Acta Anaesthesiol Scand 1993; 37:780-2.
(22) Tarumi Y, Ota K, Maeno H, Ishitani K, Namiki A. Measuring plasma concentration of morphine and its metabolites is useful for pain control in cancer patient with renal impairment. J Japan Society of Pain Clinicians 1999; 6:110-3.
(23) Hasselstrom J, Sawe J. Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. Clin Pharmacokin 1993; 24:344-54.
(24) Cramond T, Wright AWE, Stuart GS. Smith MT. Plasma and CSF concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide in cancer patients receiving morphine by the

intracerebroventricular route. Proc Seventh World Congress on Pain. Paris: IASP Press 1993:531-2.
(25) Faura CC, Collins SL, Moore RA, McQuay HJ. Systemic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998; 74:43-53.
(26) Tarumi Y, Watanabe S. Methadone [review]. Palliative Care Medicine (Japanese) 2000; 2:182-90.Ashby MA. Martin P, Jackson KA.
(27) de Stoutz ND, Bruera E, Suarez-Alamazor M. Opioid rotation for toxicity reduction in terminal caner patients. J Pain Symptom Manage 1995; 10:378-84.
(28) Ashby MA. Martin P, Jackson KA. Opioid substitution to reduce adverse effects in cancer pain management. Med J Aust 1999; 170:68-71.
(29) Kloke M, Rapp M, Bosse B, Kloke O. Toxicity and/or insufficient analgesia by opioid therapy: risk factors and the impact of changing the opioid: a retrospective analysis of 273 patients observed at a single center. Support care cancer 2000; 8:479-486.
(30) Maddocks I, Somogyi A, Abbott F, Hayball P, Parker D. Attenuation of morphine-induced delirium in palliative care by substitution with Infusion of oxycodone. J Pain Symptom Manage 1996; 12:182-189.
(31) Mercadante S, Casuccio A, Fulfaro F, Groff L, Roberto B, Villari P, Gebbia V, Ripamonti C. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. J clin Oncol 2001; 19:2829-2904.
(32) Mercadante S, Casuccio A, Calderone L. Rapid switching from morphine to methadone in cancer patients with poor response to morphine. J Clin Oncol 1999; 17:3307-12.
(33) Grond S, Radbruch L, Lehmann KA. Clinical pharmacokinetics of transdermal opioid. Clin Pharmacokiet 2000;38:59-89.

(34) Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther 1987; 41:392-401.
(35) Gorman AL, Elliott KJ, Inturrisi CE. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett 1997; 223:5-8.
(36) Ivarsson M, Neil A. Differences in efficacies between morphine and methadone demonstrated in the guinea pig ileum: a possible explanation for previous observations on incomplete opioid cross-tolerance. Pharmacol Toxicol 1989; 65:368-72.
(37) Ripamonti C, Groff L, Brunelli C, Polastri D, Stravrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain. What is the equianalgesic dose ratio? J Clin Oncol 1998; 16:3216-21.
(38) Edmonton Regional Palliative Care Program http://www.palliative.org/
(39) Bates MS, Edward WT, Anderson KO. Ethnocultural influences on variations in chronic pain perception. Pain 1993;52:101-102.
(40) Anderson R, Saiers JH, Abram S, Schlicht C. Accuracy in equianalgesic dosing: conversion dilemmas. J Pain Symptom Manage 2001; 21:397-406.
(41) Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids: a critical review and proposals for long-term dosing. J Pain Symptom Manage 2001; 22:672-87.

EXPECTATIONS OF PERIPHERAL OPIOID ANALGESIA

J.G. Collins, Ph.D.
Professor of Anesthesiology
Lecturer in Pharmacology
Yale University School of Medicine

Dr. Collins will focus on the following points during this presentation: comparison of spinal opioid analgesia with peripheral opioid analgesia; endogenous peripheral opioid analgesia; evidence for exogenous peripheral opioid analgesia; possible mechanisms of action of peripheral opioid analgesia; questions that need to be answered in order to better understand the potential for peripheral opioid analgesia as an important clinical tool for the control of pain.

Ferreira and Nakamura first proposed the existence of peripheral opioid analgesia in 1979 (1) and other labs reported similar findings almost ten years later (2,3). However those basic science studies did not produce a significant use of peripheral opioid analgesia in the clinical setting. There is disappointment that peripheral opioid analgesia has not become a widely used clinical tool with which to control pain. The limited use of peripheral opioid analgesia is contrasted with spinal or epidural opioid administration. Dr. Collins will compare the development of the two techniques and point out that such a comparison is not fair. The timing of each discovery as well as the types of pain against each can be effective differs greatly.

Stein and Colleagues have continued to pursue an understanding of the endogenous systems that mediate peripheral opioid analgesia in the absence of exogenously administered drugs. That work has produced a detailed understanding of the interactions between the immune and nervous system that appear to be responsible for a peripheral endogenous pain control system (4). An important consideration associated with Stein's work is the impact of a depressed immune system on a patient's pain. It is likely that patients with a compromised immune system may experience greater levels of pain as a result of a dysfunctional peripheral opioid analgesic system.

Although Stein and colleagues have firmly established the existence of an endogenous peripheral opioid analgesia system we are still left with questions about the possibility of influencing that system by exogenously administered opioids. Several reviews have questioned the value of exogenous peripheral opioid analgesia but they have also pointed out the significant problems that have been associated with most of the clinical trials in which the technique was examined (5-7). Because of the many problems with interpretation of most clinical trials of peripheral opioids, including lack of sensitivity of assays and inappropriate drug doses, we still do not know the true potential value of the technique but it does offer unique advantages that warrant further study. Those advantages direct targeting to sites of inflammation and possible efficacy against visceral pain, a type of pain that is difficult to treat with current methodologies.

There is evidence that the binding of opioids with opioid receptors on the peripheral terminals of primary sensory neurons causes changes in the functioning of the neurons that could impede the flow of information from the periphery to the central nervous system. Changes in G proteins and ion channels have been reported (8-10). Such changes could reduce the excitability of peripheral nerves, decrease the propagation of action potential sand reduce the peripheral release of pain producing substances. Those systems should also be sensitive to exogenously administered opioids.

Essential questions that remain to be answered about peripheral opioid analgesia include what happens to the receptors on nerve terminals to allow them to become sensitive to opioids and what is the nature of those receptors. Although inflammation is required to enable peripheral opioid analgesia it can also be induced by a hyper tonic solution. There appears to be receptor up-regulation but the time-course is much slower than the

onset of peripheral opioid analgesia. We know that mu, delta and kappa opioid receptors exist on the peripheral terminals of primary sensory neurons but we do not know if those receptors are the same as opioid receptors that have been studied in the central nervous system. In fact, there is reason to believe that there are differences in peripheral opioid receptors that may cause them to have a different pharmacological profile than classical central nervous system receptors (11, and Collins and colleagues, unpublished observations). Answers to these questions are likely to enable us to determine the maximum efficacy of peripheral opioid analgesia.

It is likely that we will be able to utilize the endogenous peripheral opioid system to produce a degree of analgesia that is greater than that caused naturally. We need to better understand how to unmask peripheral opioid receptors and we also need to have a better understanding of the peripheral receptors themselves. In addition we need the continuing support of drug development companies. It is likely that the most important advance in peripheral opioid analgesia will depend on the development of novel agonists with high affinity for peripheral receptors. Those agonists will also need to be restricted in their ability to gain access to the central nervous system. The potential value of peripheral opioid analgesia, in spite of current disappointment in its progress, warrants a continued effort to understand and develop the technique for clinical pain management.

1. Prostaglandins 18, 91-100, 1979
2. Anesth.Analg. 66, 1277-1281, 1987
3. Pharmac. Biochem. Behav. 31, 445-451, 1988
4. J. Neurosci. 22, 5588-5596, 2002
5. Pain 71, 127-134, 1997
6. Pain 72, 309-318, 1997
7. Anesth.Analg. 93, 761-770, 2001
8. Neuroscience 32, 571-575, 1989
9. J. Neurosci. 19, 8337-8348, 1999
10. Br. J. Pharmacol. 129, 110-114, 2000
11. Pain 79, 175-185, 1999

在宅ホスピス・緩和ケアにおける疼痛緩和の実際と問題点

ホームケアクリニック川越院長　川越　厚

在宅ホスピス・緩和ケアでは患者の普段の生活を第一に考え、自然な形の経過を見ながら疼痛などの患者の苦痛を緩和し、患者と家族が安心して在宅で過ごせるような安全な方法で医療を提供することが重要である。症状緩和の中心は疼痛緩和であり、その中心となる薬剤は strong opioid である。病院などの施設と違い在宅ではオピオイド使用に関してさまざまな制約と問題点があり、今回このような視点にたって当クリニックで関わった末期癌患者の疼痛緩和を紹介するとともに、その問題点について述べることにする。

当院は開業 3 年目の無床診療所であるが、在宅末期癌患者に対するホスピス・緩和ケアはグループ・バリアンを組織して学際的なチームケアの形をとってサービス提供している。平成 12 年 7 月から同 14 年 6 月までの 2 年間に 177 例の末期癌患者を在宅でケアし、死亡した 146 名のうち 140 名（95.9%）は在宅死であった。在宅死した 140 例の中でモルヒネなどの strong opioid を使用したのは 99 例（71%）であり、そのうち 80 例（57%）はモルヒネ徐放剤経口投与、44 例（31%）は経直腸投与、28 例（20%）は持続皮下投与、2 例（1%）が IVH 投与、1 例（1%）がフェンタニルパッチ投与であった。

在宅でのオピオイド使用に関する問題は①どのように説明して新規導入するか②オピオイド服用を誰が管理するか③DDS の変更（特に経口モルヒネ徐放剤から経皮的フェンタニル投与への変更）をどのように行うか、またその際どのような注意が必要か④臨死期に経口摂取が不可能となった時モルヒネ投与の継続をどのように考えたらよいか、また具体的な方法はどうあるべきか⑤モルヒネなどの廃棄方法はどうすればよいか⑥モルヒネの細やかな調整をどうすればよいか、などである。我々の対応の仕方を具体的な事例提示の中で明らかにしたい。