

Opioid Use in Cancer Pain Management in Indonesia: a Call For Attention

Rianto Setiabudy¹, Cosphiadi Irawan², Aru W. Sudoyo²

¹ Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

² Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence mail to:

Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia. Jl. Salemba 6, Jakarta 10430, Indonesia. email: rianto_set@yahoo.com.

ABSTRAK

Nyeri hebat merupakan masalah utama bagi penderita kanker dan tatalaksana nyeri seringkali membutuhkan penggunaan opioid. Indonesia merupakan salah satu negara dengan penggunaan opioid yang sangat rendah bagi pasien kanker dan hal ini perlu mendapatkan perhatian karena banyak sekali penderita kanker di negeri ini mengalami penderitaan yang tak perlu mereka rasakan akibat kurangnya penggunaan opioid.

Ketidakmampuan untuk menilai nyeri dengan baik, kegagalan untuk menentukan dosis yang tepat, kekhawatiran akan adiksi, peraturan yang terlalu ketat, semuanya turut berperan dalam gagalnya penerapan penggunaan morfin yang rasional bagi penderita kanker. Nyeri lucut (breakthrough pain) merupakan masalah yang membutuhkan perhatian khusus, tidak hanya karena masalah ini sering dijumpai, tetapi juga karena dibutuhkan pengetahuan yang baik untuk menanganinya. Hambatan-hambatan tersebut dibahas dalam tinjauan berikut ini agar dapat memberikan pemahaman yang lebih baik tentang penggunaan opioid yang tepat bagi nyeri kanker yang berat. Beberapa contoh penggunaan opioid yang tidak tepat dalam tatalaksana nyeri kanker juga dibahas.

Kata kunci: opioid, nyeri lucut (breakthrough pain), nyeri kanker, morfin.

ABSTRACT

Severe pain is a major problem for cancer patients, and pain management often requires the use of opioids. Indonesia is one of the countries where the use of opioids for cancer patients is extremely low, and this calls for attention, as many cancer patients in the country undergo unnecessary suffering as the consequence of this opioid underuse.

The inability to assess pain correctly, failure to determine the correct dose, fear of addiction, overly tight regulation, all contribute to the failure to implement rational use of opioids for cancer patients. Breakthrough pain, a problem which requires special attention not only because it is commonly found but also requires proper knowledge to handle them. These hurdles are discussed in the present review, in order to bring a better understanding about the correct use of opioids in severe cancer pain. Some examples where opioids are used inappropriately in cancer pain management are also discussed.

Key words: opioid, break through pain, cancer pain, morphine.

INTRODUCTION

Pain is very commonly found in cancer patients.¹⁻³ The management of cancer is frequently inadequate because of patients' failure to report it, poor communication between patients and health care providers, and many other reasons. Severe and chronic pain often dehumanize dying cancer patients, causing them unable to pass the last segment in their live in serenity. Poor management for cancer pain has been reported frequently.⁴⁻⁶ Ironically in fact, 90% cases of cancer pain can be alleviated with simple medical management.⁷ In all over the world, it is agreed that morphine is the opioid of choice to alleviate severe cancer pain.⁸ In well-developed countries such as Canada, USA, Denmark, Switzerland, and United Kingdom, the consumption of morphine for pain exceeded 50 mg/capita in 2009. Indonesia with the annual consumption of only 0.054 mg/capita, belonged to the countries which ranked the worst in the world. This indicates that in Indonesia, opioids are extremely underused for its correct indications.⁹ Consequently, too many cancer patients die in pain and suffering.

The aims of the present discussion is to call attention for improving the use of opioids in the management of cancer pain in Indonesia.

BARRIERS TO USING OPIOIDS FOR CANCER PAIN

There are several reasons for the inadequate use of opioids in cancer pain. Some major obstacles are, among others, incompetence of the medical staff to assess pain, patients' reluctance to express the intensity of their pain, doctors' and patients' reluctance to use opioids due to the fear of addiction, the insufficient skill and knowledge of the health care staff to use opioids for cancer pain.¹⁰ The fear of addiction is indeed groundless because when used appropriately, opioid addiction in cancer pain management occurs very rarely.¹¹ Today, opioid-producing industries are striving to develop special formulations that deter the abuse of opioid pain killers by applying physical barrier, agonist/antagonist combinations, aversion, combination, etc.^{12,13} The other hurdle, despite this is always denied by the regulatory authorities, is the difficulty to

obtain morphine due to the excessively tight and complicated regulation. In Indonesia, PT Kimia Farma is authorized to import and distribute morphine for medical use. It is not the intention of the present discussion to find the culprit of this problem, but the poor record of opioid used for cancer pain in Indonesia, as reported by the WHO, should be improved.

PAIN ASSESSMENT

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association for the Study of Pain). Inability to assess pain appropriately is the main cause of failure in management of cancer pain.¹⁴ A survey done by von Roenn et al,¹⁵ indicated that 76% medical doctors felt that they were unable to assess pain correctly. For various reasons, many cancer patients are unable to report adequately to their doctors the pain they feel. This is particularly true for the elderly, those with cognitive impairment, with language barrier, with drug addiction, or being at the end of their life.¹⁶ Cancer pain may include nociceptive, somatic, neuropathic, psychological origins or a mixture of them. Consequently, a holistic approach involving multi-disciplinary experts is often needed.

Pain assessment is done by visual analogue scale (VAS) method, i.e. by asking patient to mark a 10-cm long straight line with a pencil to indicate the severity of pain they feel. The more severe the pain, the more far to the right the patient has to mark. The accuracy to assess pain is of paramount importance for titrating the daily requirement of morphine. In this method the whole range of pain intensity is divided into a 10-grade scoring system. Pain scores of 1-3 indicate mild pain and can be treated satisfactorily with simple analgesics (e.g. paracetamol) or non-steroidal anti inflammatory drugs (NSAIDs) (e.g. ibuprofen, meloxicam, diclofenac). Pain scores of 4-6 should be treated with weak opioids (e.g. codeine, tramadol) alone or in combination with a simple analgesics or NSAID. Pain scores of 7-10 require strong opioids (e.g. morphine, oxycodone, hydromorphone, fentanyl). In all pain grades of pain, the addition adjuvants is

allowed as elaborated in the later part of this discussion.

PHARMACOTHERAPY OF PAIN

Basically, the pharmacodynamic strength of an analgesic should be matched to the pain intensity felt by the patient. This principle is implemented in the pain relief ladders of WHO.¹⁷ Ladder 1 is for mild pain (pain score 1-3), which can be treated with simple analgesics such as paracetamol or NSAIDs like ibuprofen. Ladder 2 (pain score 4-6) requires weak opioids such as codeine or tramadol. Some experts use a combination of a simple analgesic with a weak opioid to reduce side effect. For example, a fix combination of 325 mg paracetamol combined with 37.5 mg tramadol is available on the market. Ladder 3 (pain score 7-10) requires strong opioids such as morphine, fentanyl, oxycodone, etc. For patients with severe cancer pain, it is mandatory that strong opioids be used directly. In all ladders, the analgesics used may be combined with adjuvant(s). In a survey, it was reported that with proper implementation, the WHO pain ladder led to an 80% success rate in alleviating cancer pain.¹⁸

Pharmacotherapy of Cancer Pain with Opioids

In pharmacotherapy of severe cancer pain, the choice and the dose of strong opioids is determined in 2 phases. Phase 1 is for titrating the daily opioid requirement of an individual patient and this is best done by using intravenous (IV) morphine. In the Ciptomangunkusumo Hospital, Jakarta, the first step is to give a loading dose of morphine 0.05-0.1 mg/kg BW in 20 mL of saline solution intravenously in 3

minutes. Usually the pain reduction effect can be observed in 15 minutes afterwards. Then the infusion is continued by giving a total daily dose of 10 mg/24 hours for naïve patients. A total daily dose of 15 mg/24 hours is given for opioid tolerant patients. Re-assessment of pain with VAS is done in 2-hour intervals. If pain subsides, as indicated by a reduction pain score of ≥ 3 , the same dose is maintained. Otherwise, an additional 10% of total daily dose is given as an IV bolus. The additional dose may be repeated every 2 hours as required, but not to exceed 10 times in 24 hours. At the end of 24 hours, the total daily morphine requirement can be summed up and be given again in the next 24 hours. If pain is still uncontrolled, the dose can be increased in the same way. If pain is controllable, the pain management can proceed to phase 2, where the daily requirement of IV morphine from a patient is converted to a non-parenteral opioids, e.g. oral morphine tablet (immediate release, IR, or sustained release, SR), fentanyl patch, hydromorphone oral, oxycodone oral, etc.

A conversion table is available for this (**Table 1**). For example, a patient requires 20 mg of IV morphine in a day. This is converted to 60 mg of immediate release oral morphine tablets. Thus, this patient needs one 10-mg tablet every 4 hours. For patients using immediate released oral morphine, the last dose before bedtime could be doubled (i.e. 20 mg in this example) to avoid the patient being waken up during asleep.^{19,20} If slow release oral morphine is used in this case, 30 mg dose is given every 12 hours. Laxative or stool softener should be given prophylactically to avoid constipation.

Table 1. Conversion table from morphine to other opioids for cancer pain

Morphine (mg/day)		Codeine (mg/day)		Fentanyl (mcg/hour)	Oxycodone (mg/day)	Hydromorphone (mg/day)	
IV/SC	O	IV/SC	O	TD	O	IV/SC	O
20	60	130	200	25	30	1.5	7.5
40	120	260	400	50	60	3	15
60	180	390	600	75	90	4.5	22.5
80	240	520	800	100	120	6	30

Note: IV = intravenous, O = oral, SC = subcutaneous, TD = transdermal. Oxycodone and hydromorphone are not yet marketed in Indonesia.

Patients with well-controlled pain with an opioid and in stable condition may often have 2-3 episodes of pain in a day. The pain, which lasts about 30 minutes, is known as a breakthrough pain (BP). BP occurs in 64% of patients with cancer pain.²¹ Cancer pain is considered under control if BP recurs not more than 3 times in a day. Otherwise, the daily basal requirement of opioid needs to be increased. Since BP has to be alleviated immediately, the use of a fast acting opioid is mandatory. Under no circumstances slow release opioids are indicated here. In hospitalized patients, one tenth of the 24-hour morphine is given and, if necessary, this may be repeated after at least 2 hours. For ambulatory patients who are on oral morphine, a 10-20% of the total daily dose is given to alleviate the BP. Pain is then assessed in 60 minutes, and the same dose is given again if there is no response. The European Association for Palliative Care recommended the use of a morphine solution for injection for this purpose.⁸ The other choice is fentanyl buccal soluble film (SBSF)^{22,23} which

is not yet marketed in Indonesia. Anyway, slow release opioids such as fentanyl patch or slow release oral morphine should not be used to treat BP.

If an opioid has been given to a patient in a relatively high dose but the therapeutic response is disappointing, several actions could be taken. Firstly, to perform opioid rotation because different opioids may have different affinity to various opioid receptors. Secondly, to add adjuvant agents (**Table 2**). Thirdly, to apply surgical intervention or radiotherapy, especially for pain associated with bone metastasis.

If pain disappears, e.g. because of surgical intervention, and opioid is no longer needed, then administration of opioid has to be tapered off within 3-5 days. In contrast, if the pain worsens, the dose has to be increased. Unlike other therapeutic agents, opioids apparently do not have a "ceiling effect", which means one can continuously increase the dose until a desirable analgesic effect is obtained as long as it does not induce a significant side effect. Hanks et al⁸

Table 2. Adjuvant analgesics for adults/children with body weight of >50 kg³²

Type of drugs	Dose	Comment
Corticosteroids:		
- Dexamethasone	16-96 mg/day, O	for pain caused by brain metastases and epidural spinal cord compression
- Prednisone	40-80 mg/day, O	
Anticonvulsants:		
- Carbamazepine	200-1600 mg/day, O	for neuropathic pain
- Phenytoin	300-500 mg/day, O	
Antidepressants:		
- Amitriptylin	25-150 mg/day, O	for neuropathic pain
- Doxepine	25-150 mg/day, O	
- Imipramine	20-100 mg/day, O	
- Trazodone	75-225 mg/day, O	
Neuroleptics:		
- Methotrimeprazine*	40-80 mg/day, O	
Antihistaminics:		
- Hidroxyzine	300-450 mg/day, O	for anxiety and nausea
Local anesthetics and antiarrhythmics:		
- Lidocaine	5 mg/KgBW/day, IV or SC for neuropathic pain	
Psychostimulants:		
- Dextroamphetamine analgesic	5-10 mg/day, O	for enhancing opioid effect reducing sedation
- Methylphenidate	10-15 mg/day, O	

IV=intravenous, O=oral, SC=subcutaneous, *=not marketed in Indonesia

reported that analgesic dose of morphine may vary up to 1,000 times among cancer patients.

SIDE EFFECTS

In general, opioid related side effects appear at the beginning of therapy and most of them disappear spontaneously after several days. Nausea, being the most frequent side effect, can be treated with haloperidol (1.5 mg per oral at bedtime), chlorpromazine (12.5 mg per oral every 8 hours), metoclopramide (10 mg per oral every 8 hours), dexamethasone (8-10 mg intravenously). Other commonly found side effects at the beginning of treatment include drowsiness, pruritus, and urinary retention. At the later stage, the prominent side effect is constipation. In addition to high fiber intake, bisacodyl (5-15 mg per oral or 10 mg per rectal) or lactulose (1-2 spoonful per oral) or magnesium hydroxide (2-4 teaspoonful before bedtime) are useful to overcome this problem.

A strong reason causing doctors and patients denying opioid treatment is the fear of addiction. This is groundless because, in fact, addiction occurs very rarely in patient with cancer pain. In an observational study it was reported that 7 out of 24,000 patients treated with opioids became addicted.²⁴ There are two strong characteristics of addiction, i.e. compulsive reaction and craving. In compulsive reaction, the patient incessantly seeks for more opioids, regardless of the pain has been controlled. Craving is characterized by nausea, arthralgia, sweating, chilling, etc. at the time when an addict needs the drug. In the treatment of cancer pain, the increasing requirement of opioid may also caused by the progression of tumor growth rather than development of tolerance.

In Indonesia, meperidine (more commonly known as pethidine) injection is very commonly used, perhaps because it is widely available and affordable as well. In many other countries, this opioid has been abandoned in pain management because norpethidine, its major metabolite, stimulates the central nervous system and causes tremor, muscle twitching, agitation, and convulsion. This is more commonly seen if the patient gets the drug repeatedly or if the patient has impaired renal function.²⁵ The toxic

metabolite is slowly excreted out of the body due to its long half-life of elimination.²⁶

PHARMACOKINETICS AND LIMITATIONS OF MORPHINE

Morphine has some limitations related to its pharmacokinetic profile. By the oral route, only 20-30% of a given dose is absorbed and its onset of action may vary considerably between patients.²⁷ In patients with impaired renal function, one of its active metabolites, i.e. morphine-6-glucuronide, accumulates. This potent metabolite may increase morphine toxic effect in patients with creatinine clearance less than 30 mL/ment/1,73 m2).²⁸

The non-pharmacokinetic limitation of morphine is its relatively poor efficacy in alleviating neuropathic pain (opiate insensitive pain). Respiratory depression is an obvious side effect if morphine (and other opioids) is given to healthy individuals, but not in patients with chronic cancer pain. Therefore, for patients being well controlled with morphine, it is important to reduce the dose when the pain subsides substantially due to e.g., surgical intervention, radiation, nerve block, etc.^{29,30} Failure to do this may lead to respiratory depression because the morphine-induced respiratory depression at the respiratory center is no longer opposed by pain transmitted from the nociceptor.³¹

Despite of these limitations, morphine remains the drug of choice for the treatment of cancer pain because of the accrued clinical experience, its wide availability, and reasonable cost.

COMMON ERRORS IN THE MANAGEMENT OF CANCER PAIN

In many cases, cancer pain cannot be completely eliminated. By knowing the commonly done errors, however, more effective treatment can be provided to the patients. Eight commonly found errors in the treatment of cancer pain include: 1). Failure to do appropriate pain assessment; 2). Mild analgesics (e.g. mefenamic acid) are used for severe cancer pain; 3). Treatment for severe cancer pain is started with mild analgesics; 4). Slow onset of action opioids (e.g. slow release morphine, fentanyl

patch) are used to alleviate breakthrough pain; 5). Conversion to other opioids is done before the daily requirement of morphine is determined correctly; 6). Failure to consider opioid rotation, adjuvant therapy, bisphosphonate, and radiation for patients with persisting cancer pain due to bone metastasis; 7). Failure to anticipate opioid-related side effects; 8). Opioid is given only when the patients feel pain, not around the clock.

CONCLUSION

As in many developing countries, the use of opioids in Indonesia to treat cancer pain is extremely low as compared to that of the developed countries – in fact, one of the lowest. This prompts urgent actions to reduce the suffering of cancer patients such as eliminating the myth of addiction related to cancer pain treatment, improving availability and accessibility to opioids for their proper use, dissemination of technique to give opioids in the proper dosing, and avoidance of the errors commonly encountered in using opioids. The authors would like underline a glorious tenet saying that freedom of pain is one of the basic human rights.

CONFLICT OF INTEREST

The authors have no conflict of interest

REFERENCES

- Delgado-Gay MO, Bruera E. Management of pain in the older person with cancer. Part 1. *Oncol*. 2008;22:56–61.
- de Leon-Casasola OA. Current developments in opioid the therapy for management of cancer pain. *Clin J Pain*. 2008;24:S3–S7.
- Ahmedzai S. New approaches to pain control in patients with cancer. *Eur J Cancer*. 1997;33 suppl;6:S8-14.
- Yennurajalingam S, Braith F, Bruera E. Pain and terminal delirium research in the elderly. *Clin Geriatr Med*. 2005;21:93-119.
- Mercadante S, Arcuri E. Pharmacological management of cancer pain in the elderly. *Drugs Aging*. 2007;24:761-6.
- Dalal S, Del Fabbro E, Bruera E. Symptom control in palliative care - part 1: oncology as a paradigmatic example. *J Palliat Med*. 2006;9:391–408.
- Jacox A, Carr DB, Payne R. New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med*. 1994;330:651-5.
- Hanks GW, de Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain. The EAPC recommendations. *Brit J Cancer*. 2001;84:587-93.
- Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2009.
- Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med*. 1993;119:121-6.
- McQuay H. Opioid in pain management. *Lancet*. 1999;352:2229-32.
- Raffa RB, Pergolizi Jv. Opioid formulations designed resist/deter abuse. *Drugs*. 2010;70:1657-75.
- Katz NP, Adams EH, Chillcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*. 2007;23:648-60.
- Herr K, Titler MG, Schilling ML, et al. Evidenced based assessment of acute pain in older adults: current missing practices and perceived barriers. *Clin J Pain*. 2004;20:331-40.
- Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med*. 1993;119:121-6.
- Loftus LA, McIntosh, J, Peace E, Tolsen D. Implementation of SIGN 44 guidelines for managing cancer pain in a community setting. *Internat J Palliat Nursing*. 2007;13:315-24.
- World Health Organization. *Cancer Pain Relief 1966*. WHO: Geneva, 1966.
- Jadad MR, Browman GP. The WHO analgesic ladder for cancer pain management. *J Am Med Assoc*. 1995;274:1870-73.
- Twycross RG. Control of pain. *J R Coll Physicians Lond*. 1994;18:32-9.
- Regnard CFB and Badger C. Opioids, sleep and the time of death. *Palliat Med*. 1997;1:107-10.
- Portenoy RK and Hagen NA. Breakthrough pain: definition, prevalence, and characteristics. *Pain*. 1990;41:273-81.
- Delgado-Guay MO. Efficacy and safety of fentanyl buccal for cancer pain management by administration through a soluble film: an update. *Blick SK, Wagstaff AJ. Drugs*. 2006;66:2387-93.
- Rauk R, North J, Gever LN, Tagarro L, Finn AL. Fentanyl buccal soluble film (SBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol*. 2010;21:1308-14.
- Friedman DP. Perspective on the medical use of drugs of abuse. *J Pain Symp Manage*. 1990;5:S2-S5.
- Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidenberg M. Accumulation of norperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med*. 1977;86:738-41.

26. Latta KS, Ginsberg B, Barkin RL. Meperidine: A critical review. *Am J Ther.* 2002;9:53-68.
27. Glare PA and Walsh TD. Clinical pharmacokinetics of morphine. *Ther Drug Monit.* 1991;13:1-23.
28. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. *Pain.* 1998;74:43-53.
29. Hanks GW, Twycross RG, Lloyd JW. Unexpected complications of successful nerve blocks. *Anesthesia.* 1981;36:37-9.
30. McQuay HJ. Potential problems using both opioids and local anesthetic. *Br J Anaesth.* 1988;61:121.
31. Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. *Pain.* 1996;64:123-28.
32. Jacox ARN, Daniel B, Carr DB, Payne R. New Clinical-Practice Guidelines for the Management of Pain in Patients with Cancer. *N Engl J Med.* 1994;330:651-5.