Management of Pain in Cancer through WHO Three-Step Analgesic Ladder

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Introduction

The World Health Organization(WHO) launched a cancer pain relief programme in 1986, as one of the WHO's four priorities in its comprehensive cancer control programme[1]. The other three are cancer prevention, early detection linked with curative treatment, and implementation of national cancer control programmes in each member state. The objective of the WHO Cancer Pain Relief Programme is to offer adequate pain relief to all cancer patients in the world by the year 2000, through the existing health care system.

Cancer Pain Management Status in The Wwold

One out of every 8 deaths in the world is due to cancer[2]. In far advanced stages, 70% of cancer patients experience pain, of which 80% are severe and persistent. Cancer pain has been commonly under treated and frequently neglected as a public health problem in developed as well as in developing countries[1]. Even in the medically affluent areas of the world, 50 to 80% of cancer pain patients are not satisfactorily treated[1,3]. Cancer pain is hardly treated at all in many developing countries. A conservative estimate is that globally at least 4 million people are presently suffering from cancer pain with little or no relief[2].

Reasons for Inadequate Pain Relief

The reasons why cancer pain is not adequately treated in most countries are summarized by the WHO in 1984 as follows[1]:

□ A widespread lack of recognition by health care professionals of the fact that established methods already exist for satisfactory cancer pain management.

□ A lack of concern by most national governments.

□ A lack of availability in many areas of the world of the drugs essential for the relief of cancer pain.

□ Fears concerning psychological dependence both in doctors and in the public if strong opioids are more readily availlable for medical purposes.

□ A lack of systematic education of medical students, doctors, nurses and other health care

professionals about cancer pain management.

WHO Cancer Pain Relief Programme

In 1980, cancer pain relief was made one of the four priorities in the WHO's cancer control programme by the Cancer and Palliative Care Unit, WHO Headquarters, Geneva.

In 1982, a WHO Consultation on Cancer Pain Relief brought together in Milan 17 experts from 9 countries[1]. These experts prepared a draft set of guidelines on the relief of cancer pain. These guidelines expressed the consensus that, using a limited number of drugs, pain relief was a realistic target for the majority of cancer patients throughout the world.

In 1982 to 1984, the Saitama Cancer Center in Japan tested the guidelines. In this study, 87% out of 156 cancer patients with pain ultimately became pain-free with minimal side-effects[4].

Since 1985, five centers in five different countries with different health care systems have published the results of field-tests of the WHO guidelines[4~8]. In each of the studies, it has been demonstrated that, for the majority of cancer patients, pain can either be reduced considerably or completely controlled by the use of analgesics alone or in combination with adjuvant drugs. Thus, the cross-cultural feasibility and effectiveness of the WHO guidelines was more clearly demonstrated.

In 1984, a WHO Meeting on Comprehensive Management of Cancer Pain was held in Geneva with 24 international experts in the field of pain, cancer pain, drug regulation and pharmaceuticals. This meeting resulted in the publication of the WHO monograph, Cancer Pain Relief[1]. It includes the modified 1982 guidelines, entitled Method for Relief of Cancer Pain.

The monograph has been best-selling WHO publication which is now available in 22 different languages. It is the second most translated publication in WHO history. In the Western Pacific region, it has been translated into Chinese, Japanese, Malay and Vietnamese. The monograph is clearly fulfilling a need.

The WHO Method emphasizes that analgesic drugs are the mainstay approach to managing cancer pain. The WHO Method can be applied everywhere in the world, i.e., not only in sophisticated hospitals but also in medical settings at community level anywhere in the world, as long as currently needed drugs and well-trained health care professionals are available.

The WHO Method for Relief of Cancer Pain

The WHO monograph describes the nature of cancer pain, its assessment, state-of-the-art therapeutic strategy for cancer pain management, legislative factors, substance abuse, education and training, and, in the form of an annex, the WHO method.

The basic drugs listed in the WHO Method comprise four different groups. The drug list was revised by the WHO Expert Committee held in Geneva in July 1989(Table 1 and 2).

Group 1 is the non-opioid group which includes aspirin, paracetamol and other non-steroidal anti-inflammatory drugs.

Group 2 is the opioid group for mild to moderate pain, namely weak opioids. The parent drug is codeine.

Group 3 is the opioid group for moderate to severe pain, that is, strong opioids. The parent drug is morphine. Several alternatives are shown in the list but some of them are availalbe only in some countries.

Group 4 comprises adjuvant drugs, namely, opioid antagonists, anticonvulsants, antidepressants, neuroleptics, and corticosteroids. They

Table 1. A Basic Drug List for Cancer Pain (WHO 1989)

Category	Standard drugs	Alternatives
Non-opioids	acetylsalicylic acid paracetamol ibuprofen indomethacin	choline magnesium trisalicylate diflunisal fenoprofen naproxen
Opioids for mild to moderate pain	codeine	buprenorphine dextropropoxyphene dihydrocodeine oxycodone standard opium
Opioids for moderate to severe pain	morphine	hydromorphone levorphanol methadone oxycodone pethidine
Antidepressants Anticonvulsants Corticosteroids	amitriptyline carbamazepine prednisolone dexamethasone	imipramine valproic acid betamethasone prednisone

should be added to non-opioid and opioid medications if there is a specific indication(Table 2).

As shown in the WHO three-step analgesic ladder(Fig. 1), the first step should be to use a non-opioid drug. If, in the recommended dosage and frequency, this is not effective, a drug in the weak opioid group should be added to the non-opioid medication given. When a weak opioid in combination with a non-opioid fails to relieve pain, a strong opioid should be used. Of course, therapy can be started on from any of these three steps according to the intensity of the patient's pain.

Among strong opioids, morphine is accepted as the classic, best-studied drug, and its use in cancer pain management has been recommended by prestigious expert groups, because it is simple to administer and when properly used, it provides effective pain relief in most cancer patients. But this simple fact is not fully understood by many health care professionals.

Five key concepts in the WHO Method under-

Table 2. Adjuvant drugs

	Adjuvant drugs(WHO 1986)					
	Analgesic effect	Antidepressant effect	Anxiolytic effect	Muscle relaxant	Antiemetic	Anti-confusional
Anticonvulsants						
carbamazepine	+[a]					
phenytoin	+[a]					
Psychotropicdrugs						
prochlorperazine			+			
chlorpromazine			+	(+)	+	
haloperidol			+		+	
hydroxyzine	+		+		+	+
diazepam			+	+		
amitriptyline	+[b]	+	(+)			
Corticosteroids						
prednisolone	+[c]	(+)				
dexamethasone	+[c]	(+)				

[a]Often of benefit in lancinating(shooting, stabbing) pain.
[b]Often of benefit in dysaesthetic(superficial burning) pain.
[c]Often of use in nerve compression, spinal cord compression, raised intracranial pressure.

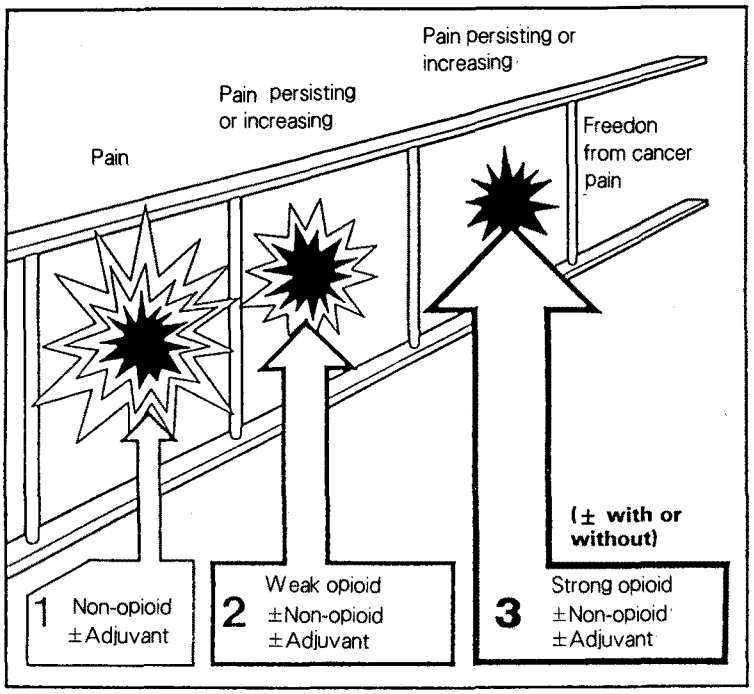

Fig. 1. The WHO three-step analgesic ladder.

lying the use of analgesics in cancer pain management are "by mouth", "by the individual", "by the clock", "by the ladder" and "attention to detail". These concepts are based on the premise that doctors should learn how to use a few potent drugs well:

By mouth

Drugs should preferably be given by mouth. Oral administration helps the paitient be independent. But, in certain situations, a drug might have to be given sublingually, rectally or by injection.

By the individual

The dose of an analgesic should be determined on an individual basis. The right dose is the dose that relieves the patient's pain for a reasonable period of time, preferably four hours or more. The dose should be titrated against the patient's pain, gradually increasing until the patient is comfortable.

By the clock

The dose should be given on a regular basis by the clock. In this way, it is possible to relieve the pain continuously, and, as demonstrated in Fig. 2, it is possible to keep plasma concentration of an analgesic at the effective, non-toxic level. "As required" administration should be avoided.

By the ladder

If a drug is ineffective, another drug that is definitely stronger should be prescribed(Fig. 1). The use of strong opioids, namely morphine, should be dictated according to the intensity of pain, and not according to the brevity of prognosis.

Attention to detail

Side-effects must be treated systematically. Once therapy is started on, cancer patients need close supervision to achieve maximum comfort and minimal side-effects should be monitored,

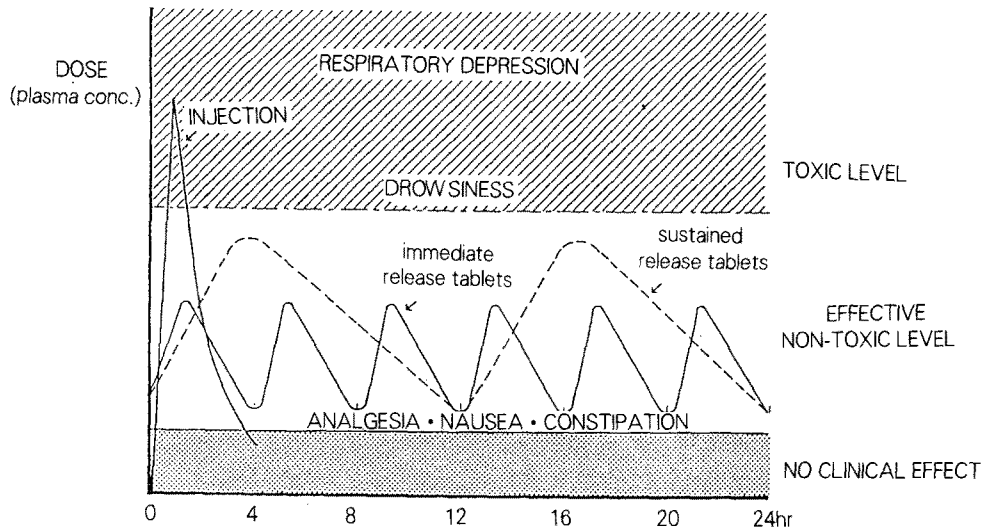

Fig. 2. Diagram to illustrate the results of regular 4 hourly oral morphine, 12-hourly slow-release morphine tablets, one shot injection of morphine, plasma concentration of the drug and clinical effects.

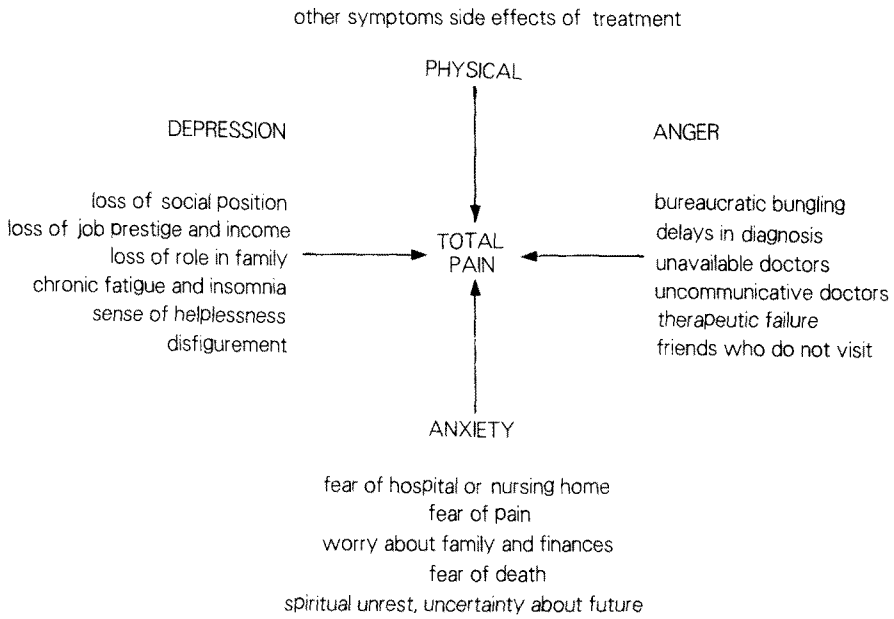

Fig. 3. Factors influencing pain sensitivity of cancer patients(cited from Twycross RG, Lack SA: Therapeutics in Far-Advanced Cancer. 2nd Ed, Churchill Livingstone, 1990).

and attention should always be paid to the patient's psychological state, since in patients with advanced cancer, psychological factors are the major influence in determining the severity of pain(Fig. 3).

The WHO method relies upon the concurrent and sequential use of a series of treatment procedures which must be adapted to needs of the individual patients. All pain is not equally responsive to analgesics. For instance, neuropathic pain such as post-herpetic neuralgia may not be relieved by the use of an analgesic, but often responds to a tricyclic drug. In a small number of patients neurolytic blocks and neurosurgical procedures may be necessary as a supplementary approach. A palliative radiotherapy is often effective, especially for bone pain.

A Sequence of Specific Aim

Excellent pain relief is not always obtained immediately after the treatment is started. In practice, a sequence of specific aims is useful:

☐ increase the hours of pain-free sleep;

☐ relieve the pain when the patient is at rest;

☐ relieve pain in standing or during activity.

While complete pain relief is not always possible, the WHO method can be used to help all patients considerably. In many ways this method is merely an outline. The details are likely to vary from country to country and from patient to patient.

Impact of WHO Activity

Since 1986, the WHO has had various activities to implement the programme. WHO proposals to the member states include[2]: establishment of a policy and programmes on cancer pain relief and palliative care; provision for the priority for the training of health care professionals in cancer pain relief and palliative care; assistance in the international exchange of educators; inclusion of cancer pain management as a compulsory subject in courses leading to certification; ensuring that drug legislation does not prevent cancer patients from receiving the drugs necessary for pain relief; and incorporation of cancer pain relief programmes into existing health care systems.

The WHO Headquarters and six WHO Regional Offices have provisions to assist member states in establishing national cancer pain relief programmes and making oral morphine available. Several missions by WHO consultants have been sent to a number of developing countries including China, India, Viet Nam, Papua New Guinea, and the Philippines. The missions have helped those countries establish national policies and provide a teaching curriculum to educate doctors and nurses. Discussions were also initiated with the health policy makers about making oral morphine available. The WHO supports publication of native language versions of the monograph, Cancer Pain Relief, in some developing countries.

These WHO activities reflect recent improvements in cancer pain management in many countries. The governments of Australia, Canada, China, Finland, France, India, Japan, Mexico, Netherlands, Philippines, Sweden and Vietnam have established national policies which include guidelines on cancer pain management[9].

Many other member states which include Argentine, Chile, and Papua New Guinea are now providing their national policies. The State of Wisconsin and other states in the United States have begun initiatives in cancer pain management.

A number of developing countries which include China, India and Brazil have recently made oral morphine available for the first time

for cancer pain relief.

There are currently eight WHO Collaborating Centers related to cancer pain relief established in Milan, Oxford, Wisconsin, Amsterdam, Manitoba, Saitama, New York and Alberta; all eight are successfully contributing to worldwide programme implementation.

Thus, close international collaborative ties have been developing between govermental and non-governmental organizations, medical centers and/or experts.

Mass communication networks have frequently reported on the WHO programme. Many articles have appeared in the world's major newspapers and magazines. A number of major television broadcasting networks have aired programmes on cancer pain relief. These mass communication activities have played an invaluable role in encouraging higher public expectations for effective cancer pain management.

Future Challenges

For the past several years, health care professionals in all parts of the world have been increasingly making efforts to correct this common problem[2]. To succeed in programme implementation, it is essential to disseminate existing knowledge that can be applied throughout the world and to make currently needed analgesics, especially morphine, available in each country. WHO has outlined three criteria[2]. These are policies, teaching and training, and opioid availability in each country. All three are important and interdependent with each other, so that achievements in two areas without the third will severely limit the effect of the programme.

Policy

Establishment of a cancer pain relief policy by national governments should be a key priority in each member state's health care system or as part of its cancer control activities. The formulation of a policy is central to a concerted effort to allow for adequate cancer pain relief, opioid availability, and education of health care professionals. At present, the governments of Australia, Canada, China, Finland, France, India, Japan, Mexico, Netherlands, Philippines[10], Sweden and Vietnam have definite national policies.

Education and Training

There are still so many doctors, nurses, other health care workers and health policy makers in the world who are not aware of the importance of cancer pain relief, since there is widespread inadequacy in medical education in cancer pain management. Medical students are taught to treat cancer, and not to treat pain. It is very encouraging to note that several governments and leading medical societies have issued reports on cancer pain in recent years[1,2,4~8,10], and have held workshops or seminars on cancer pain relief. The WHO would like to have the outstanding pain experts from all over the world to focus their unique knowledge, skills and resources on the great task of educating health care professionals in each country in successful implementation of the cancer pain relief and palliative care programmes.

Widespread undue fear of the dangers of psychological dependence among doctors, nurses, patients and the wider public is one of the major impediments to programme implementation. Misunderstanding and undue anxiety of tolerance, physical dependence and psychological dependence and lack of understanding of the latest knowledge of the clinical pharmacology of opioid analgesics have caused many doctors to use opioid analgesics in inadequate doses

and sometimes to avoid their use altogether. There are currently no clinical evidence which supports this reluctance among docters. Neither tolerance nor physical dependence limits the doctor's ability to effectively use opioid drugs in cancer pain management, provided that the drugs are used correctly[1,2]. Wide clinical experience has also shown that psychological dependence rarely if ever occurs in cancer patients receiving opioids for persistent pain[1,2].

Opioid Availability

Sufficient quantities of those drugs in the basic drug list, especially oral morphine, must be made available in each country. The global problems of drug abuse and illegal trafficking make the WHO programme implementation tougher.

Global demands for morphine have more than doubled in recent years as a result of increasing oral administration of morphine for pain relief. However information available to the United Nations International Narcotics Control Board (INCB) suggests that the need for opiates for legitimate medical purposes is not being fully met [11]. Only a few countries have established effective and comprehensive systems for assessing that need and monitoring the extent to which it is met.

In fact, informal information collected at the Second International Congress on Cancer Pain, held in New York in 1987, and information obtained thereafter reveal that oral morphine for medical purposes is not available at all in 9 out of 19 participating developing countries, mainly due to strict legislative regulations.

The INCB report for 1989[11] states that reactions of legislators and administrators to the fear of drug abuse developing, the manner in which drug control laws and regulations are interpreted or implemented, limitations within health care systems, public perceptions of the potential danger of psychological dependence, and the medical practice and attitudes of health care professionals, unduly impede the availability of opiates.

The INCB's recommendations to member states include[11]: examining the extent to which the health care systems, laws and regulations permit the use of opiates for medical purposes; identifying possible impediments and developing plans of action to facilitate the supply and availability of opiates for all appropriate indications; establishing national policies on the treatment of conditions for which opiates may be indicated; and ensuring the health care professionals receive sufficient education and up-to-date training in the use of opiates.

In the final paragraph of the report, it is stated that medical instructors, and professional associations of physicians, pharmacists, nurses and pharmaceutical manufacturers should be urged to promote rational use of opiates for medical purposes, bearing in mind their responsibility to ensure that opiates will not be abused. Together with the WHO, the INCB jointly prepared guidelines for opioid availability for medical purposes.

These recommendations will reflect the improvement of accessibility of morphine for cancer pain relief. In 1989, the Philippines' Dangerous Drug Board amended two regulations in order to implement the national policy on cancer pain relief[10]. Japan revised the Narcotics Control Law in 1990 and 1991. In 1991, Chinese goverment legalized oral morphine for the first time for the national cancer pain relief programme implementation.

Conclusion

The WHO Expert Committee on Cancer Pain

Relief and Active Supportive Care held in Geneva in July 1989 recommended that WHO expand the cancer pain relief programme to encompass the management of other common problems that physically, psychologically, socially and spiritually afflict cancer patients and their families[2]. WHO will strengthen its activities to achieve freedom from cancer pain and other symptoms.

Every year, about seven million new cancer patients are diagnosed, and about five million die[12]. The global prevalence of cancer is estimated to be 14 million. If present trends continue, the incidence of cancer will rise in almost all parts of the world. For a long time to come, many patients will probably continue to be diagnosed with cancer that is beyond the curable stage[12]. The goal here must be to provide adequate pain relief and palliative care as soon as possible.

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Appendix: Use of Oral Morphine According to The WHO Method for Relief of Cancer Pain

Role and Pharmacological Characteristics of Morphine in Cancer Pain Management.

Morphine is the parent drug of the strong opioids which should be used to relieve moderate and severe pain. Morphine is accepted as the classic, best-studied drug, and its use in cancer pain management has been recommended by prestigious expert groups, because it is simple to administer and provides satisfactory pain relief in 80~90% of patients with cancer and pain. According to the author's clinical experience, 80% of cancer patients with pain need morphine prescription to relieve their pain during their disease progression[4].

Morphine has a variety of pharmacological actions. However, a very small amount of morphine has no clinical effect. When slightly increased in dose, pain-killing effect is clinically manifested(Fig. 2). Simultaneously, nausea is complained of by more than one-third of the patients receiving the doses, and constipation by almost all the patients. Nausea can be controlled with concurrent use of an antiemetic and constipation with a laxative. If increased more in dose, the patient become drowsy. With further increase in dose, respiratory depression may result. But such a high dose is unnecessary to control cancer pain. Administration of a certain dose of morphine by one shot injection, however, results in a higher plasma concentration of the drug than oral administration. The unnecessarily high plasma concentration induces the risk of danagerous adverse effects. If doses much larger than the analgesic dose are repeately given, psychological dependence may result.

Effective analgesic dose of morphine is a dose that relieves pain for four to five hours but does not make the patient drowsy. Sustained release morphine tablets are available in varying strength. The tablets provide much convenience for the patient, since the tablets need only 12 hourly oral intake to maintain continuous pain relief.

Morphine has a relatively short half-life, and its pharmacodynamics are linear, so that it is simple to titrate morphine against intensity of the pain in individual patients. Morphine has no ceiling effect. The effective pain-killing dose of morphine varies considerably in individual patients and ranges from as little as 30 mg/day to more than 1,000 mg/day. According to the clinical experiences in the United

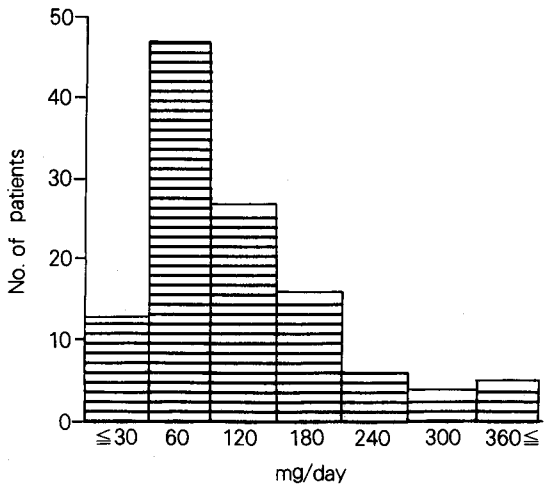

Fig. 4. Morphine in daily dose that relieved of pain in 118 Japanese cancer patient.

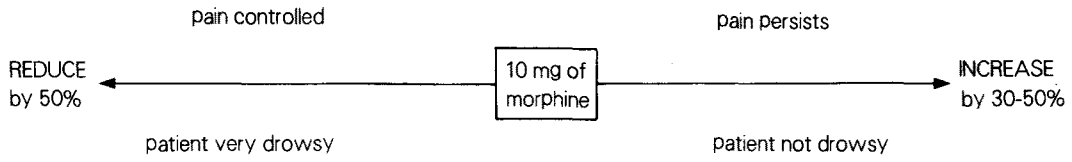

Fig. 5. Dose adjustment of morphine according to the effect.

States and Japan, however, pain in most cancer patients with pain has been controlled with a daily dose of below 240 mg/day(Fig. 4). Doses of 1,000 mg or more were appropriate in only a few percentage of the patients. Thus, the dose varies greatly for different patients because of wide individual variation in the oral bioavailability of the drug. It is hardly possible to predict the appropriate effective dose of morphine before it is given. Therefore, the starting dose should be small and the dose should be titrated against the patient's pain, gradually increasing it until the patient is comfortable.

Use of Morphine in Cancer Pain Management

Suggested starting dose of oral morphine is 10 mg every four hours(60 mg/day). In an elderly and debilitated patients, 5 mg(30 mg/day) may be appropriate. Next day, the analgesic effect as well as unwanted adverse effects should be assessed. If patient is extremely drowsy and pain-free, reduce the dose by 50%. If pain persists and the patient is not drowsy, increase morphine in dose by about 50% (Fig. 5). Meanwhile, the starting dose should be repeated more frequently than 4 hourly to avoid excessive pain. The first and last doses of the day are anchored to the patient's waking and bedtimes. The best additional times during the day are generally 10 : 00 a.m., 2 : 00 p.m. and 6 : 00 p.m., With this schedule, there is an optional balance between duration of the analgesic effect and severity of unwanted adverse effects. The drug should be given through the night, or in a larger dose at bedtime, to sustain the plasma level of the drug within the effective range. With a 50% or 100% increase in the dose at bedtime, many patients do not need a further dose in the middle of the night.

Evidence found in clinical practice revealed that the equianalgesic ratio of the sustained release morphine tablets to immediate release oral morphine preparations(powder, aquenous solution, immediate release tablets, etc) was 1:1, so that half of the daily dose should be given every 12 hours. Sometimes the patients(10% or less) need 8 hourly administration of the tablets.

Morphine can be given per rectum as effectively as by mouth. If morphine suppositories are not available, morphine aquenous solution should be given per rectum every 4 hours. When morphine is given by injection, one-half of the oral dose should be prescribed. In this situation continuous subcutaneous infusion using portable infusion pump is recommended. With the use of this procedure, discomfort of repeated needle insertions are avoided, and effective plasma concentration of the drug is maintained.

Several factors should be considered when systemic morphine administration does not satisfactorily control the pain. They include underprescribing, inadequate control of the unwanted adverse effects, opioid resistant pain and psychosocial problems the patient suffers from.

Control of Unwanted Adverse Effects

Control of the unwanted effects is essential to maintain the repeated administration of morphine in cancer pain management. An anti-emetic should be prescribed during first two weeks of the morphine administration to prevent morphine-induced nausea and vomiting. A laxative, e.g., sennoside, should be prescribed to avoid morphine-induced constipation as long as morphine is given, adjusting the dose

according to the result obtained. Drowsiness, unsteadiness and mild confusion may be complained of by some patients in the initial few days of morphine administration, especially by elderly and debilitated patients. But, they will clear up within 3 to 5 days on constant doses.

Respiratory depression rarely occurs with the appropriate analgesic dose of morphine. Other unwanted adverse effects should also be controlled with specific medications. As stated before, both tolerance and physical dependence will not be a clinical problem, and psychological dependence (addiction) rarely if ever occurs in cancer patients receiving morphine for persistent pain, as long as the drug is used correctly.