

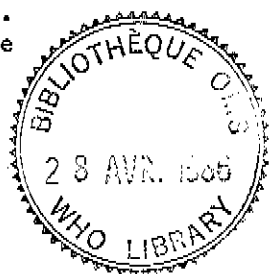
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RESULTS OF FIELD-TESTING IN JAPAN
OF THE WHO DRAFT INTERIM GUIDELINES ON RELIEF OF CANCER PAIN

by

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Summary

The World Health Organization (WHO) has a programme to globally propose a practical guideline to offer adequate pain relief to cancer patients which can be administered by the existing health care system, and has prepared the WHO Draft Interim Guideline Handbook on Relief of Cancer Pain. This Handbook provided a clear plan on the use of "a few potent analgesics" (aspirin, codeine, morphine and alternatives) and adjuvant drugs: the "WHO three-step analgesic ladder" for cancer pain relief. Drugs should be given in a stepwise approach, from nonnarcotic to strong narcotic analgesics, and "by the clock", not "as required". In the field-testing of the guidelines at the Saitama Cancer Centre, Japan, a total of 156 consecutive cancer patients with pain were treated, and 136 (87%) out of them were ultimately pain-free with minimal side effects. Aspirin (and paracetamol) was given in 86 cases and relieved cancer pain in 29 (33%). In 59 in which a nonnarcotic was ineffective, codeine was added to the medication, and pain relief was achieved in 28 (47%). Morphine was administered by mouth every four hours in 118 cases, of which 98 (83%) showed complete pain relief. Results thus indicate excellent feasibility and effectiveness of the WHO Draft Interim Guidelines. Its usefulness in relieving cancer pain in every area of the world seems promising.

Introduction

The World Health Organization (WHO) has a programme which globally proposes a practical guideline for offering pain relief to cancer patients which can be administered by the existing health care system. This programme is called the "WHO Cancer Pain Relief Programme". In 1982, a WHO Consultation (17 experts from nine Member States) prepared the WHO Draft Interim Guidelines Handbook on Relief of Cancer Pain (1). Field-testing of these guidelines has started under the aegis of the WHO Collaborating Centres in Milan and Boston. The global implementation of the programme will be effected in 1986-1990. The purpose of this paper is to report the preliminary result of the field-testing in Japan of the WHO Draft Interim Guidelines on Relief of Cancer Pain.

Aim and Background of the WHO Cancer Pain Relief Programme

Even in medically affluent areas of the world, a significant proportion of cancer patients with pain are not given adequate pain relief (2,3) despite the fact that efficient measures exist and the cost is not expensive. Misplaced fears of the dangers of dependence and addiction lead doctors to under-prescribe and nurses to under-dose. Lack of education of doctors and nurses is one of the other problems. The subject of cancer pain relief is poorly covered in most medical school curricula and in cancer textbooks (2). In recent years, medicine has become so oriented towards prevention and cure of cancer that incurable cancer patients are often regarded as failures. In the majority of cancer treatment centres, every procedure which is aimed at cure of cancer is performed with the best efforts, whereas care of physical and psychological problems from which cancer patients are suffering is surprisingly inappropriate and sometimes lacking. The need of action on pain relief is particularly critical in developing countries.

The aim of the WHO Cancer Pain Relief Programme is to disseminate the latest information of adequate analgesic treatment of cancer pain which can be utilized by the existing health care system both in developed and developing countries. The goal is to share this knowledge with all cancer victims in the world certainly by the year 2000, or as immediately as possible.

Strategies and principles of treatment

Physical pain in cancer patients can be grouped according to the causes (4): 1. pain caused by cancer; 2. pain associated with cancer therapy; 3. pain caused by debility; and 4. pain unrelated to cancer. Doctors may need to make a differential diagnosis, but to the patients, pain is still persistent pain, regardless of its cause, and it is the pain which they wish to be treated.

When pain becomes persistent, the best treatment is to identify the cause of the pain and to treat it with radiotherapy, chemotherapy or palliative surgery. If there is no available treatment for the cause of the pain, the management of pain becomes the doctor's primary

objective. While the nature and cause of the pain are being assessed, therapy should be started with analgesic drugs. In most parts of the world drugs are the mainstay in cancer pain treatment and the first choice therapy. Drugs are effective in a high percentage of patients, if they are used correctly - the right drug in the right dose at the right time interval.

The WHO Draft Interim Guidelines on Relief of Cancer Pain (1) provide clear practical advice on the use of potent pain relief drugs and on the fundamental strategies for non-pain specialists in their care of cancer patients with pain.

The strategies and principles laid out below, must be applied whenever any available analgesic drugs are used for cancer pain:

1. It is best to learn how to use a few potent drugs well;
2. The drugs should be given by mouth at regular intervals "by the clock". The next dose should be given before the effect of the previous one has fully worn off;
3. "As required" administration should be avoided. It will never be able to relieve persistent cancer pain successfully enough to erase the patient's memory and fear of the pain;
4. The aim is to titrate the dose of the analgesic against the patient's pain, gradually increasing the dose until the patient is pain-free. That is to say, doses should be determined on an individual basis;
5. If one drug is ineffective, another drug that is definitely stronger should be prescribed. It is useless to transfer to an alternative drug of similar strength;
6. The use of narcotics such as morphine should be dictated according to the intensity of the pain, and not according to the amount of time the patient has to survive;
7. It may be necessary to use several adjuvant drugs together with nonnarcotic and narcotic analgesic drugs for specific indications.

Basic drugs in the WHO Draft Interim Guidelines

According to the WHO Draft Interim Guidelines on Relief of Cancer Pain (1), the drugs which are to be used for relief of pain in cancer patients comprise four different groups (Tables I and II). The three basic analgesics are aspirin, codeine and morphine, but it is necessary to be familiar with one or two alternatives for use in patients who cannot tolerate the standard preparations.

Table I. Analgesic drugs in the WHO Draft Interim Guidelines

Category	Parent Drug	Alternative Drug
Nonnarcotic group	Aspirin 250-1000 mg 4-6 hourly	Paracetamol
Weak narcotic group	Codeine 30-130 mg 4-6 hourly	Dextropropoxyphene
Strong narcotic group	Morphine 5-30 (200) mg 4 hourly	Methadone Pethidine Buprenorphine Hydromorphone Levorphanol Standardized opium

Table II. Adjuvant drugs in the WHO Draft Interim Guidelines

Class effect	Analgesic effect	Anti-depressant effect	Anxiolytic relaxant	Muscle effect	Antiemetic effect
Anticonvulsant					
carbamazepine	+ ¹				
phenytoin	+ ¹				
Psychotropics					
chlorpromazine			+	(+)	+
prochlorperazine			+		+
haloperidol			+		++
hydroxyzine			+		+
diazepam			+	+	
amitriptyline	+ ²	+	(+)		
Steroids					
Corticosteroid					
prednisolone	+ ³	(+)			
dexamethasone	+ ³	(+)			
medroxyprogesterone	+ ⁴				

1. Often of benefit in lancinating (shooting, stabbing) pain
2. Often of benefit in dysaesthetic (superficial burning) pain
3. Often of use in nerve compression, spinal cord compression, raised intracranial pressure
4. May have benefit in pain from hormone-dependent tumours

Aspirin and morphine can be given per rectum as effectively as orally when oral intake is difficult or impossible. Subcutaneous or intramuscular injection should be used when patients are unable to take oral or rectal drugs. Injection promotes dependence of patients on the person administering the drug (5).

The parent drug in the nonnarcotic group is aspirin, and the alternative drug is paracetamol (acetaminophen). Aspirin should be given orally every four to six hours in a dose of 250 to 1,000 mg, preferably with certain antacids.

The parent drug in the weak narcotic group is codeine, which should be given orally in a dose ranging from 30 to 130 mg with a nonnarcotic drug such as aspirin.

The parent drug in the strong narcotic group is morphine. Morphine should be given by mouth every four hours in a dose ranging from less than 5 mg to 30 mg or more, up to more than 200 mg. The suggested starting dose is 5 mg to 10 mg. The effective analgesic dose of morphine varies considerably in different patients because of wide individual variation in oral bio-availability; the appropriate dose is the one that works adequately. The starting dose should be increased by 50% if, after 24 hours on the medication, there is insufficient analgesia. The patient should be reassessed after 48 and 72 hours preferably by the doctor, and if needed, the dose is readjusted on an individual basis. Morphine should be given through the night or in a larger dose at bedtime to sustain the plasma level of the drug in an effective range. With a 50% or 100% increase in dose at bedtime many patients requiring less than 60 mg of morphine do not need a middle-of-the-night dose.

These parent drugs should be available everywhere in the world. Several alternatives are suggested in the guidelines for both the weak and strong narcotic groups (Table I), but, unfortunately, some of these alternatives are unavailable in certain countries; for example, dextropropoxyphene, methadone, hydromorphone and levorphanol are not available in Japan.

The sequence in which these drugs are used should follow the course and severity of the pain. As shown in the WHO three-step analgesic ladder (Fig. 1), the first step should be to use a nonnarcotic drug (Step I). If this is ineffective, a drug in the weak narcotic group should be added to the medication (Step II). When a weak narcotic fails to relieve pain, a strong narcotic should be used instead (Step III). Each patient must be supervised as often as possible to ensure that treatment continues to match the pain and to minimize the side effects. Occasionally there is a marked psychological component to pain and an anxiolytic or antidepressant may be indicated. If no therapy produces pain relief, a search should be initiated for other factors contributing to the pain complaints. Non-pharmacological procedures of pain treatment should be considered when analgesic treatment fails to relieve pain, or when there is a specific indication.

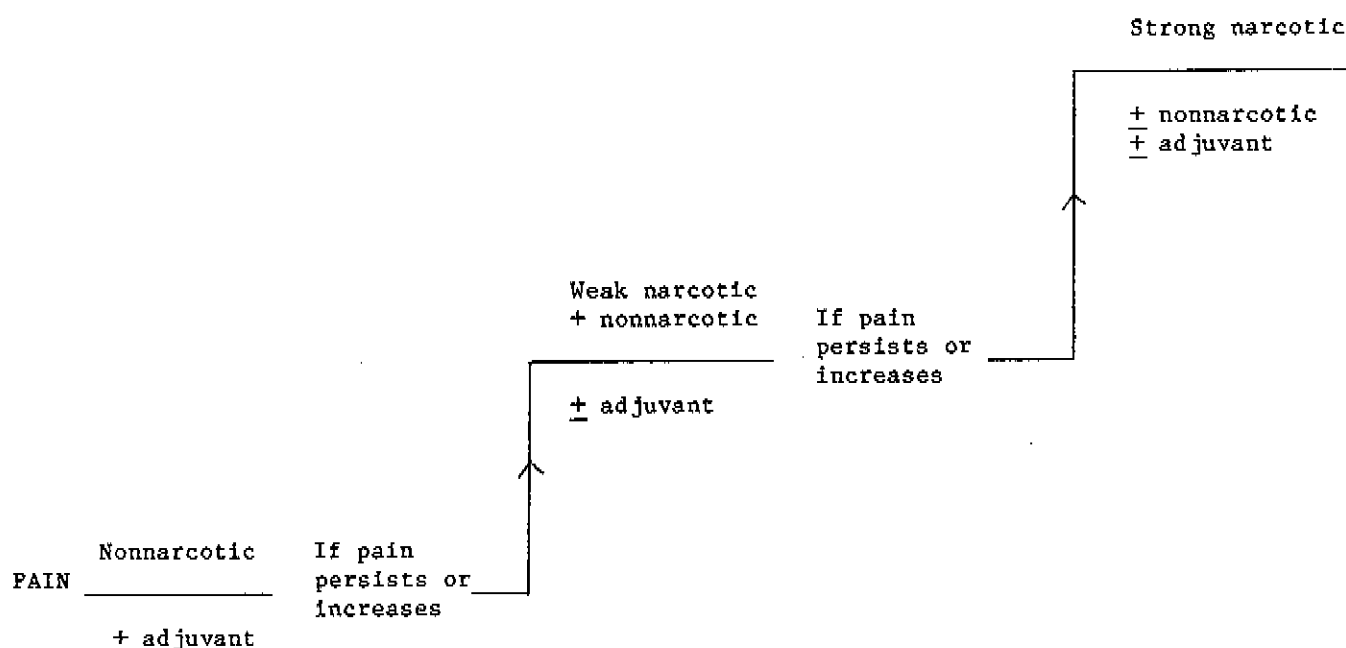


Fig 1. Three-step analgesic ladder in the WHO Draft Interim Guidelines

Adjuvant drugs, the fourth group of the drug list (Table II), should be added to nonnarcotic and narcotic drugs if required for specific indications, e.g., fears, anxieties and depression. These adjuvant drugs are anticonvulsants, antiemetics, anxiolytics, antihistamines, antidepressants, and steroids. These drugs may also be added to counteract certain side effects of the analgesics. Laxatives are almost always necessary when patients receive narcotics.

Results of the field-testing in Japan

In the field-testing of the WHO Draft Interim Guidelines, which was carried out at the Saitama Cancer Centre, a total of 156 consecutive cancer patients with pain had been treated by June 1984. The major cancer types are shown in Table III. The age of the patients ranged from eight to 83 years. In 81% of the patients, cancer had been disseminated and in 11% it was at a terminal stage. Some patients complained of multiple pains and there was 184 pains to be treated overall. The most frequent site of pain was the lower body including abdomen, followed by the head and neck (Table IV). Two-thirds of the pains were severe; 82% of the pains were caused by cancer, 8% were associated with cancer therapy, and 10% were unrelated to cancer.

Table III. Major cancer types in patients with pain treated through the use of the WHO three-step analgesic ladder

Cancer type	No. of cases
Head and neck	24 (15%)
Gastrointestinal	49 (31%)
Lung	28 (18%)
Breast	13 (8%)
Uterus	4 (2%)
Prostate	5 (3%)
Haematological	17 (11%)
Other	16 (10%)

Overall 156

Table IV. Site of cancer pain in patients treated through the use of the WHO three-step analgesic ladder

Site	No. of pain
Head and neck	41 (22%)
Upper extremities	10 (5%)
Lower extremities	17 (9%)
Trunk	37 (20%)
Upper body	24 (13%)
Lower body	50 (27%)
Generalized	5 (3%)

Overall 184 pains

Pain relief was evaluated according to the patient's self assessment of pain at each follow-up assessment, using the the modified LASA PAIN RELIEF SCORE. Complete relief means that the pain disappeared. Acceptable relief means that the pain was relieved by more than 90% according to its grade and the patient expressed satisfaction. Partial relief means a decrease of pain in grade.

Pain relief through the use of nonnarcotic analgesics

(Step I; Table V): A nonnarcotic drug was given for one to 250 days (median value + S.D. = 25.6 + 39.7) in 86 cases of mild and moderate pain, and in a few instances of severe pain. Aspirin was given in 80 cases and paracetamol in six cases, every four to six hours. Adjuvant drugs were used in 30 cases. Pain was completely relieved in 29 cases (33%), and relieved acceptably in 10 (12%). In 47 cases, either partial relief or no relief was reported. Of these, 55 cases later went on to Step II, and four with severe pain to Step III, because a nonnarcotic drug was ineffective or ceased to be effective.

Table V. Cancer pain relief results through the use of the WHO three-step analgesic ladder

Drugs	I Nonnarcotic (Aspirin)	II Weak narcotic (Codeine)	III Strong narcotic (Morphine)	Ultimate results
No. of cases (with adjuvant)	86* (30)	59** (24)	118 (21)	156
Pain Relief				
Complete relief	29 (33%)	28 (47%)	98 (83%)	136 (87%)
Acceptable relief	10 (12%)	11 (19%)	14 (12%)	14 (9%)
Partial relief	37 (43%)	15 (24%)	6 (5%)	6 (4%)
No relief	10 (12%)	5 (8%)	0	0

* Paracetamol was given in 6 cases

** Paracetamol was given in 12 cases and aspirin in the others

Pain relief through the use of weak narcotic analgesics

(Step II; Table V): In 59 cases, codeine and nonnarcotic medication were given for one to 200 days (29.0 ± 41.9). In two of these cases analgesic treatment started with Step II since the cancer pain had insufficiently responded to a previous use of nonnarcotics; they were not given regularly "by the clock". Complete pain relief was achieved in 28 cases (47%), and acceptable relief in 11 cases (19%), but partial relief or no relief was reported in 15 and five cases, respectively. Of the 59 cases on Step II, 46 later went on to Step III because the combined weak narcotic and nonnarcotic medication was ineffective or ceased to be effective.

Pain relief through the use of strong narcotic analgesics

(Step III; Table V): Morphine was administered by mouth in 118 cases, every four hours for a period ranging from three to 256 days (50.4 ± 57.3). Of these cases, 68 complained of severe pain and morphine was the first analgesic to be given. The maximum dose of oral morphine in each case ranged from three to 120 mg, but, in 86% of the cases, it was less than 30 mg. In 30% of the patients, aqueous morphine solution was given per rectum. Complete relief was reported in 98 patients (83%), but some of these patients complained of mild recurrent pain elicited by physical movement. Acceptable relief was obtained in 14 (12%), and partial relief in six cases. Fourteen patients who obtained acceptable relief were satisfied with the results of pain relief and no further treatment was given. The reason pain relief was only partial in two of the cases was apparently the result of the patients' complicated psychological state; in one a severe pain in the unilateral lower limb was caused by invasion of the lumbosacral plexus by cancer of the prostate gland, which was accompanied by a disturbed venous return, and neither neuroadenolysis nor epidural spinal block with lidocaine was again effective. The reason that relief was partial in the other four cases was that those patients had died before the doses could be increased enough to relieve their pain completely.

Side effects

(Table VI): One of the side effects of oral aspirin (Step I) noted in six patients was gastric hemorrhage despite concomitant administration of certain antacids for more than a month; these patients were given an alternative analgesic. In the weak narcotic group (Step II), there were no notable side effects. In the strong narcotic group (Step III), nausea was the most frequent side effect and was noted in 21 cases (18%) in the initial phase of the morphine administration. In most cases, however, nausea was alleviated with an antiemetic

medication. Drowsiness, unsteady gait and slight confusion were temporarily observed in some elderly patients; but, in most cases these symptoms disappeared after a few days due to the use of morphine without increasing the dose. Morphine intolerance (epigastric fullness causing persistent intermittent vomiting, pruritus, general malaise, etc.) was noted in three patients.

Table VI. Side effects of analgesics

Drugs	Side effects	No. of cases
Nonnarcotic	Gastric problems	6
	Prolonged bleeding time	0
	Allergic reaction	0
Weak narcotic		0
Strong narcotic	Nausea	21
	Drowsiness	16
	Unsteadiness	11
	Confusion	5
	Constipation (severe)	5
	Retention of sputum	5
	Morphine intolerance	3
	Withdrawal symptoms	1
Psychological dependence	0	

The use of oral morphine was discontinued in 12 patients with a gradual decrease in dose, without any manifestation of withdrawal symptoms, after the cause of the pain was successfully treated with radiotherapy. Withdrawal symptoms occurred in one patient because of a rapid decrease in dose. There was no report of psychological dependence.

Ultimate results of the WHO three-step treatment of cancer pain

(Table V): Briefly, 25 cases were treated by Step I, 11 by Step I and II, 46 by Step I, II and III, four by Step I and III, two by step II, and 68 by Step III. Almost all of the patients were given analgesic drugs until the day of their death. There were four cases which were subjected to neuroadenolysis during or after analgesic treatment, mainly because of the hormone-dependent nature of the tumour. Thus, faithful application of the WHO Draft Interim Guidelines on Relief of Cancer Pain ultimately resulted in adequate relief of cancer pain in 136 patients out of 156 (87%). Of these patients, 21 were discharged from the hospital with adequate effect from the analgesic medication to enjoy their home life. When cancer pain relief was achieved and maintained it made the patient a more cheerful person and greatly improved their quality of life. Side effects were minimal and temporary.

Discussion

It is estimated that globally one out of ten deaths are due to cancer. Yearly 5.9 million new cancer cases in all forms are diagnosed throughout the world and 4.3 million die of cancer (6). On the basis of knowledge available today, WHO predicts that - given the right measures, sufficient resources and continued goal-directed research - up to one-third of existing cancers could be avoided through primary and secondary prevention, that up to one-third can be cured, and that the remaining one-third would enter the health system too late to benefit from the optimal use of cancer therapies, but nevertheless could be spared all unnecessary physical and psychological suffering (7). Thus, WHO has three main goals in its active global cancer control programme: prevention of cancer, cure of cancer through early detection, and cancer pain relief.

Essentially, cancer is a chronic somatic disease, but it influences the patient's psychological state as the physical symptoms progress through the body. Among these, pain is the most frequent physical symptom experienced by cancer patients. It is also important to realize that pain is not a specific symptom of terminal cancer (4), but it frequently occurs as well in patients at any stage of cancer. Sufficient control of cancer pain is the first step that doctors should take to improve the quality of life for cancer patients. Cancer pain can and must be treated irrespective of stage of the disease. Doctors should keep in mind that the ideal goal of cancer pain treatment is to make the pain disappear, not merely reduce the severity of pain.

Recently an overview of the latest knowledge on the use of potent analgesic drugs for management of cancer pain was excellently summarized by Twycross (5,8). Persistent cancer pain requires preventive therapy. Analgesics should be given regularly at a dose determined on an individual basis by clock, not by the patient's demand. Maximum or recommended doses, derived mainly from postoperative parenteral single-dose studies, are not applicable in cancer pain control. Morphine or an alternative strong narcotic drug should be prescribed when nonnarcotic and weak narcotics fail to relieve pain. The severity of the pain should determine the choice of analgesic, not the doctor's estimate of life expectancy.

The use of strong narcotic analgesics is associated with development of tolerance and physical dependence. They are normal pharmacological responses to the chronic use of these drugs. But tolerance and physical dependence do not interfere with the effective use of these drugs (9-12), provided that the drug is administered according to the rules and principles described above. Although undue concern and fear of dependence has caused doctors and nurses to use these drugs in inadequate dose, several studies (8,10,11) have clearly shown that psychological dependence rarely, if ever, occurs in cancer patients receiving narcotics in the right dose at the right time interval for chronic pain. It should also be emphasized that chronic use of oral morphine can be discontinued with a gradual decrease in dose, without any manifestation of withdrawal symptoms. One to three weeks may be necessary to gradually decrease the dose before the withdrawal of oral morphine.

Pain is a somatopsychic experience; there are also emotional and psychological aspects, and many patients become demoralized and show anxieties and depressed states which enhance the pain. If it is not appreciated, the pain remains intractable. It is for this reason that in addition to the analgesic drugs certain other agents are prescribed for specific indications. Anxiolytics and antidepressants are necessary in a significant proportion of patients with pain although they are not recommended for routine use.

The fundamental strategies described in the WHO Draft Interim Guidelines are the consensus of the world experts and authorities on cancer pain relief. The drugs described have been used successfully throughout the world. The WHO Guidelines, which are scheduled to be finalized within a couple of years, will globally offer clear practical advice on the adequate use of potent analgesic drugs in treatment of cancer pain to doctors, nurses and other health care personnel. Cancer patients, their families as well as the general public will also be made aware that cancer pain can certainly be controlled.

Conclusions

The field-testing in Japan of the WHO Draft Interim Guidelines on Relief of Cancer Pain resulted in an adequate relief of pain in a considerably high percentage of cancer patients. It indicates the excellent feasibility and effectiveness of the WHO Guidelines. The value of the WHO Guidelines in relieving cancer pain in every area of the world seems promising.

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