· *Original Article*

A Retrospective Study on the Use of Oral Morphine in Cancer Pain

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Abstract

The authors report a retrospective study of 390 cancer pain patients tested with oral morphine during a four-month period. Initial pain scores were reduced to one half after one week of treatment and then maintained throughout the study period. Mean daily dosages of morphine were lower in those patients 65 years and older. No significant changes in performance in relation to therapy were noted except for an increase in hours of sleep. An accurate titration of dosage and continued control of side effects are the main requirements of this method of administration. The presence of side effects and the cause of interruption of treatment are reported. J Pain Sympt Manag 1987;2:77–81.

Key Words
Oral morphine, cancer pain, opioid analgesia

Introduction

The use of oral morphine in cancer pain has been adopted in thousands of cases throughout palliative care units, hospices, oncological centers, and in home care of patients with advanced cancer. The works of Twycross,[1] Saunders,[2] Mount,[3] Hanks,[4] Walsh,[5] Foley,[6] and Ventafridda[7] have shown that progressive individualization of drug therapy enables maximum effectiveness to be obtained without any adverse effects, and achieves a noticeable reduction in pain without lowering patients' performance.

The approach to treatment may be explained through the bioavailability of the drug. The bioavailability of oral morphine has been evaluated by several authors, and the data available are not homogeneous. While Gourlay et al[8] have found the bioavailability of oral morphine to be 26% ± 13% (average ± SD, range

10%–43%), higher values, 38% ± 17% (average ± SD, range 15% to 64%), have been reported by Sawe et al.[9] Individual variability in the bioavailability of the orally administered drug and also its plasma half-life (1.2 to 4.9 hours according to Gourlay et al)[8] justify the necessity to individualize the dosages by means of a gradual increase in doses and frequency of administration. The optimum treatment may vary from the classic every four hourly. It should be remembered also that the plasma concentration of the drug in steady state shows linear correlation to dose,[10] so that the gradual increase in dosage does not lead to disproportionate rises in the plasma concentration. The relation between plasma concentration and the analgesic effect is also noticeably variable from patient to patient and represents another factor in favor of oral titration of the drug.[8,10–12]

This method of administration requires the use of drugs against nausea, vomiting, and constipation. Moreover, the central effect of morphine can be usefully integrated, in some types of cancer pain, with non-steroidal anti-inflammatory drugs (NSAIDs), which have a peripheral action. [13]

The World Health Organization (WHO) and important international medical societies[14,15] advocate this type of administration as a first choice treatment for patients with cancer pain who require the use of strong opioid medication. The therapeutic strategy put forward by WHO[16] proposes the use of analgesics as the principle treatment in a three-step ladder. According to this method, morphine is used after non-narcotic and "weak" narcotic drugs, in association with adjuvant drugs (eg, psychotropics, steroids, and NSAIDs). When this method is not tolerated, the drug is administered by alternative routes, either parenteral or spinal.[17] In pain syndromes in which morphine is not effective[18] and pain is localized, nerve blocking is suggested as an alternative. Having followed this guideline for many years, we consider it opportune to report our experience concerning the use of oral morphine.

Clinical Experience

In the Pain Therapy Division at the National Cancer Institute, the use of oral morphine in water solution varying from 0.2% to 1% has been used for more than ten years in patients who no longer benefit from "weak" opioids before passing to parenteral methods and who have no problems with oral ingestion (eg, gastrointestinal intolerance or obstruction). On the basis of our clinical experience and from data collected from our evaluation team, we report a retrospective analysis of a sample of patients treated with oral morphine in our service.

Materials and Methods

A retrospective study was carried out on 390 patients (216 male; 174 female) treated at the Pain Therapy Division of the National Cancer Institute of Milan. All had pain due to advanced cancer. The average age of the patients was 58.9 ($\pm$ 0.6 SE) years. Clinical data are listed in Table 1. All patients were treated with oral morphine solution when their pain was no longer controlled with "weak" opioids and NSAID administration, following the WHO sequential ladder.[15,16] Patients selected for study underwent morphine treatment for more than one week. Morphine solution was administered every four hours. The majority of

patients were administered non-steroidal anti-inflammatory drugs and adjuvant drugs (neuroleptics, antidepressants, benzodiazepines, anti-convulsants, or steroids) for the control of concomitant symptoms. The initial daily mean morphine dose was 67 mg ($\pm$ 2 SE).

Data for this study were collected daily. A pain evaluation form has been in use which integrates the information contained in the oncological clinical file, where pre-codified and descriptive information are recorded. Data are recorded from the first examination to death, or until the end of oral morphine administration. A daily recording form is completed at the home of the patient, with the help of relatives, if necessary. This form records: the daily duration of pain at five different levels of intensity;[19] hours of sleep; performance status;[20] hours standing; hours sitting; and presence or absence of major side effects.

The daily recording form is explained to the patient at the first visit and checked afterwards during follow-up by the nurse in the hospital or by the home care nurse once a week. The nurses, who conduct the first interview before the patient is examined by the doctor, assess the intensity of the patient's pain using five key words: slight, troublesome, exhausting, terrible, and excruciating; the patient is able to describe the progress of his pain over a 24-hour period. The exact value to be attributed to these key words has been established numerically beforehand.[19] In fact, to obtain a daily pain score, the hours of pain (described with one key word) are multiplied by a corresponding factor (slight = 1, troublesome = 2.5, exhausting = 5, terrible = 7.5, excruciating = 10) and then totaled. With this method the obtainable scores range from 0 to 240, although the scores of a majority of patients rarely exceed 100. We also collect

Table 1
Primary Cancer Pathology

Cancer Pathology	N
GI tract	117
Lung	98
GU tract	69
Breast	65
Pancreas	18
Bone	12
Unknown	6
Central nervous system	5

personal and social data, information about the analgesic treatment being administered (including drugs and dosages), type of pain and its location, primary and secondary oncological disease, type of care, and previous or current anticancer therapy. Every 20 days during the study the causes of interruption of the treatment were recorded (Table 2).

Table 2
Causes of Interruption
of Oral Morphine Treatment

Days	Total No. Patients	Interrupted Due to Side Effects or Inefficacy	Died (No. Patients)
1	390	—	—
20	297	41	52
40	206	4	87
60	154	2	50
80	114	2	38
100	91	—	23
120	73	—	18

All data are entered into a computer with a data base management system which integrates data entry, inquiry, information retrieval and interface with programs for graphic and statistical elaboration.[21] In this study, we analyzed the mean daily pain scores and daily morphine dosage for a period of 120 days. The time course of performance status, hours of sleep, and standing and sitting hours were analyzed by one-way ANOVA. The value of each side effect was expressed by the percentage of days in which it was present during the time of observation.

Results

The mean daily pain scores demonstrated a fall of over 50% in the basic values (Fig 1). This was already evident during the first ten days and progressively fell to less than one third of the initial values during a period of 30 days. The course of the pain score subsequently became irregular but was maintained, however, well below the mean initial value of 52 (± 2 SE). The reasons for the interruption in treatment, as shown in Table 2, explain the observation that only 73 patients were still under evaluation on the 120th day.
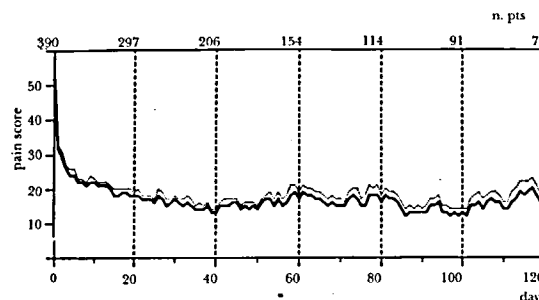

Fig 1. Mean daily pain scores during a four-month period. The solid line represents mean values, and the dotted line stands for standard errors (SE).
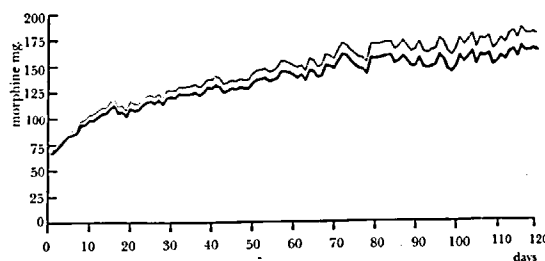

Fig 2. Mean daily oral morphine dosage. The solid line represents mean values, and the dotted line stands for standard errors (SE).
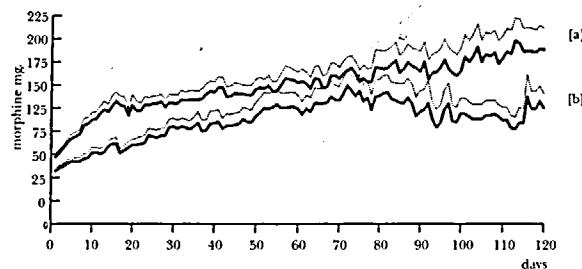

Fig 3. Mean daily dosage of morphine in patients aged 21 to 64 years (a) and 65 or older (b). The solid line represents mean values, and the dotted line stands for standard errors (SE).

A constant trend can be noted in the mean daily morphine dosage of the 390 patients (Fig 2). The mean value, calculated over the entire observation period, is equal to 134 mg (± 23 SD). Variations in the mean dosages of morphine were also compared between patients aged 21 to 64 years (n = 243) and those 65 or older (n = 147). Fig 3 indicates the higher mean daily dosage taken by the younger patients, with the mean of this group 149 mg (± 26 SD) and that of the older group 110 mg (± 21 SD).

No significant variations occurred in the scores for performance, hours standing, and hours sitting, while hours of sleep increased by two to five hours from the mean value of six hours at the start of treatment (Table 3).

Table 3
Change in Quality-of-Life Measures with Oral Morphine Therapy

Quality-of-Life Measures	Before Therapy	Range During Morphine Therapy
Performance status	51	43–50
Standing hours	2	1–2
Sitting hours	4	3–5
Sleeping hours	6	8–11

Fig 4 demonstrates the incidence of side effects as a percentage of daily occurrence from the observations available for each patient. An analysis of the relationship between doses and side effects (in particular nausea and vomiting, which are the chief reason for treatment interruption) indicates that symptoms diminish with doses above 270 mg/day (Table 4).
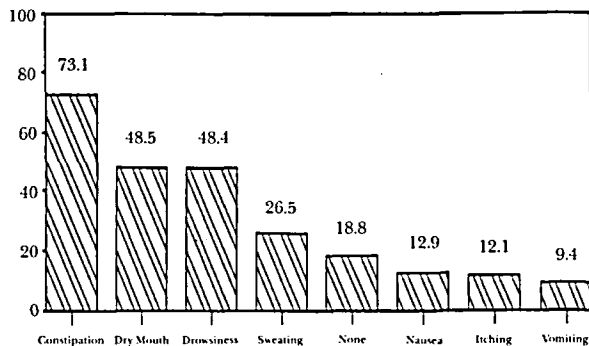

Fig 4. Percentage of days in which side effects were present in 390 patients.

Table 4
Percentage of Patients with Nausea and Vomiting with Reference to Morphine Dose

Daily Dosage	Nausea	Vomiting
30 to 120mg	25%	10%
121 to 270mg	19%	11%
more than 270mg	6%	9%

Discussion

It can be seen from these data that morphine reduced initial pain symptoms by up to one third. The discontinuity of the curve (Fig 1) shows that increases in pain can occur during treatment, which could be due to the emergence of a new painful lesion with an inadequate amount of morphine or to the occurrence of pain not sensitive to this drug[18]. This course of morphine dosing also demonstrates the classic effect of tolerance, although the need for higher doses diminished after the 60th day of treatment and tended to form a plateau (Fig 2). In addition, when patients aged 21 to 64 years were compared to older patients a clear difference in the need for morphine was observed; this is in accordance with the literature demonstrating reduced morphine clearance in the latter group.[22]

The palliative effect obtained from morphine therapy is considerable, although the performance scores were not altered by the therapy. The increase in hours of sleep which did occur represents a primary objective of the treatment strategy for these patients.[1] Regarding side effects, nausea and vomiting both had a low incidence; the further decrease with higher dosages is due to the fact that such patients either tolerate the drug better or that a better control has been reached with adjuvant therapy. Table 2 indicates that the ineffectiveness of the drug or the presence of uncontrollable side effects is mostly evident in the first 20 days of treatment, thus determining the need to adopt alternative modalities of administration. Other common side effects of morphine included constipation and drowsiness. The latter represents a phenomenon which may be refractory; considering the analgesic effects obtained, however, life activity in general was usually not significantly impaired by this effect. The initial difficulty in tolerating morphine represents a significant problem. A proportion of patients (10% to 20%) do not accept the side effects of the drug even with a correct approach to therapy. This also supports the need for careful titration of the drug to obtain an individualization of dosage for each patient and limit the number of patients unable to tolerate the drug.

Oral administration of morphine could not be maintained for the majority of patients to the last hours of life due to their aggravated clinical condition. Parenteral infusion of mor-

phine was then necessary.

In conclusion, the oral administration of morphine should be considered within the context of multimodal treatment provided within an organization of patient care based on the continuous monitoring of pain and other symptoms. In the sphere of home care assistance, the education of the patient and family in the use of morphine and other adjuvant drugs is fundamental. Given present knowledge, the methodology of drug administration presented here appears extremely valid and undoubtedly remains one of the main therapeutic instruments for cancer pain control.

Acknowledgement

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