Original Article

Low Morphine Doses in Opioid-Naive Cancer Patients with Pain

Sebastiano Mercadante, MD, Gianpiero Porzio, MD, Patrizia Ferrera, MD, Fabio Fulfaro, MD, Federica Aielli, MD, Corrado Ficorella, MD, Lucilla Verna, MD, Walter Tirelli, MD, Patrizia Villari, MD, and Edoardo Arcuri, MD

Anesthesia & Intensive Care Unit and Pain Relief and Palliative Care Unit (S.M., P.F., P.V.), La Maddalena Clinic for Cancer, Palermo; Departments of Anesthesiology and Intensive Care (S.M.) and Medical Oncology (F.F., W.T.), University of Palermo, Palermo; Medical Oncology Department (G.P., F.A., C.F., L.V.), University of L’Aquila, L’Aquila; and Intensive Care and Pain Therapy Unit (E.A.), National Cancer Institute Regina Elena, Rome, Italy

Abstract

Cancer pain can be managed in most patients through the use of the analgesic ladder proposed by the World Health Organization. Recent studies have proposed to skip the second “rung” of the ladder by using a so-called “strong” opioid for moderate pain. However, usual doses of strong opioids commonly prescribed for the third rung of the analgesic ladder may pose several problems in terms of tolerability in opioid-naive patients. The aim of this multicenter study was to evaluate the efficacy and tolerability of very low doses of morphine in advanced cancer patients no longer responsive to nonopioid analgesics. A sample of 110 consecutive opioid-naive patients with moderate-to-severe pain were given oral morphine at a starting dose of 15 mg/day (10 mg in those older than 70 years). Doses were then titrated according to the clinical situation. Pain intensity, morphine doses, symptom intensity, quality of life, and the requirement for dose escalation were monitored for a period of 4 weeks. The treatment was effective and well tolerated by most patients, who were able to maintain relatively low doses for the subsequent weeks (mean dose 45 mg at Week 4). Only 12 patients dropped out due to poor response or other reasons. The use of very low doses of morphine proved to be a reliable method in titrating opioid-naive advanced cancer patients who were also able to maintain their dose, in a 4-week period, below the dose level commonly used when prescribing strong opioids. J Pain Symptom Manage 2006;31:242–247. © 2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

WHO method, cancer pain, opioids, morphine

Introduction

Cancer pain management is based on the use of the three-step analgesic ladder proposed by the World Health Organization (WHO). The main aim of the WHO guidelines was to legitimize the prescribing of so-called “strong” opioids, a goal arising from evidence of poor management of cancer pain.
due to the reluctance of health care professionals, institutions, and governments to use opioids because of fears of addiction, tolerance, and illegal use. The application of the WHO three-step analgesic ladder has been reported to provide satisfactory pain relief in up to 90% of patients with cancer pain.

Despite the large experience proving the feasibility and efficacy of the analgesic ladder, in the years of evidence-based medicine, the three-step ladder has been criticized for the lack of robust data supporting this approach. Studies validating the WHO analgesic ladder had methodologic limitations including the circumstances during which assessments were made, small sample sizes, retrospective analyses, high rate of exclusions and dropouts, inadequate follow-up, and a lack of comparison with levels of analgesia before the introduction of the analgesic ladder.

The role of so-called “weak” opioids in the treatment of moderate cancer pain also has been questioned, and it has been speculated that Step 2 of analgesic ladder could be bypassed. Previous studies underlined the role of opioids for moderate pain (namely, codeine, dextropropoxyphene, and tramadol), in comparison with morphine, in terms of efficacy and adverse effects. In opioid-naive patients, a more favorable balance between side effects and analgesia occurred when Step 2 opioids were compared to low doses of morphine used to omit the second step. However, the comparison was based on doses of morphine that could be considered relatively high in opioid-naive patients, who are likely to be prone to adverse effects. The aim of this study was to evaluate efficacy and tolerability of very low doses of morphine, never used before for these purposes, in opioid-naive patients with cancer pain.

Methods

A multicenter prospective study was carried out in a sample of 110 consecutive advanced cancer patients with pain. Informed consent and institutional approval were obtained. Inclusion criteria were moderate-to-severe cancer pain (more than 4 on a numerical scale from 0 to 10, see below), unresponsive to Step 1 analgesic ladder drugs (nonopioid drugs), and a Karnofsky Performance Status score of 50 or more. Exclusion criteria were patients with poor renal or hepatic function, history of drug abuse, cognitive failure, and short expected survival.

Each patient initially received immediate-release oral morphine at 15 mg daily, divided in four to six doses. Patients over 70 years received initially lower doses (10 mg). Extra doses of 1/6 of the daily dose were allowed for breakthrough pain during opioid titration. Morphine doses were adjusted to maintain adequate relief without dose-limiting toxicity, considering the extra doses required in the calculation. Nonopioid analgesics were continued, if tolerated by patients. Adjuvant drugs were used according to clinical need and department policy (for example, gabapentin in daily doses increased from 300 to 1200 mg in a week, for a prominent neuropathic pain, metoclopramide in doses of 30 mg/day orally for nausea and vomiting, senna two to four tablets per day for constipation). Drugs and doses were stopped or changed according to clinical need. Patients were visited or contacted at least at weekly intervals to change therapy, according to the clinical situation.

The following parameters were recorded before starting the study (T0), 1 week after (T1), and 4 weeks after (W4):

- Pain intensity was monitored using a numerical scale from 0 to 10.
- Symptoms caused by opioid therapy or commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, and dry mouth, were rated using a scale from 0 to 3 (not at all, slight, a lot, severe). Constipation was evaluated as follows: 0 = stool in the previous 24 hours; 1 = 2 days before; 2 = 3 days before; 3 = 4 or more days before, or need for enema.
- Quality of life was measured with Spitzer score (five items including activity, daily living, health, support, outlook, from 0 to 2, for a maximum score 10), which is a well-validated system. The interval for dose stabilization was considered the day when patients had their pain intensity controlled (less then 4/10) with acceptable adverse effects.
- Morphine escalation index percent (MEI%) was calculated at W4. This score expresses
the mean increase of opioid dosage percent from morphine starting dose (MSD), according to the following formula: \[\frac{(MMD - MSD)/MSD}{days} \times 100\], where MMD is the maximal dose of morphine. MEI in mg (MEI mg) was calculated as the mean increase of morphine dosage in milligram using the following formula: \[\frac{(MMD - MSD)}{days}\].

- The pain syndromes were considered on the basis of clinical history, anatomical site of primary tumor and distant metastases, physical examination, and investigations such as CT scan and MRI, when necessary.

Statistical Analysis

Frequency analysis was performed using Chi-squared tests. The paired Wilcoxon signed-rank test was used to compare pain intensity scores and symptom intensity scores in the four weekly periods, while the paired samples Student’s t-test was used to compare opioid mean dose in the four weekly periods. The one-way analysis of variance was performed to evaluate differences in pain mechanisms, in MEI%, in MEI mg between primary cancers. \(P\) values less than 0.05 were considered statistically significant.

Results

The mean age of patients surveyed was 62 years (range 34–83). Sixty-four patients were women, and 38 were over 70 years. Primary cancer was in the following rank order: lung 22%, breast 18%, colon-rectum 15%, urogenital 10, head-neck 9%, and others 26%.

Ninety-five patients were followed for 4 weeks. Twelve patients required alternative treatments (switching to other opioids and/or routes) due to an unfavorable balance between analgesia and adverse effects, and three discontinued morphine for different reasons. Dose stabilization was achieved within a median time of 2 days after starting morphine. Data regarding opioid doses, MEI%, and MEI in mg are reported in Table 1.

Significant differences in morphine doses were observed at W1 and W4 (\(P < 0.01\)). Mean MEI% and MEI mg were 9.8% and 1.7 mg, respectively. Significant changes were also observed in constipation and dry mouth after starting morphine. These symptom intensities persisted 4 weeks after. For the other symptoms, no relevant changes were found. Similarly, changes in quality of life did not attain significance, although a trend in improvement was recorded (Table 1). No differences were found in MEI when considering the pain mechanism or the primary cancer. No age differences were observed in pain and symptom intensity. However, older persons required significantly lower mean doses of morphine at W4, 38 vs. 50 mg (\(P < 0.01\)).

Laxatives were the most frequent drugs prescribed with morphine (95%) and antiemetics were used in 34% of patients. No correlation with the morphine dose was found. The pain mechanism did not significantly influence the parameters examined. Gabapentin was used in 12 patients with neuropathic pain. In this group of patients, mean doses of morphine did not differ, although the low number of patients did not allow further analysis.

Discussion

Although morphine has been used for years as the opioid of choice for cancer pain management, the outcomes associated with starting very low doses of morphine have never been published. Morphine used at very low doses in opioid-naïve patients may offer advantages, including a greater tolerability during dose titration while providing effective analgesia. The rationale was to replace opioids commonly used for moderate pain with morphine used in doses equivalent to the range of the flexible doses of second rung drugs commonly prescribed in clinical practice. The approach was prospectively evaluated in a sample of consecutive advanced cancer patients, including very old patients. The treatment proved to be feasible, effective, and well tolerated, and to yield an acceptable dose escalation for the period of study.

Patients receiving this approach were titrated and achieved stabilization in a couple of days, and doses were slowly increased 4 weeks after starting the therapy, with acceptable MEIs. Of interest, tolerability was excellent, with a low number of patients who discontinued morphine and required alternative drugs (about 14%). Expected adverse effects were limited and in most cases self-limited in time.
No changes in quality of life were observed after starting morphine, as it was observed in tolerant patients who were prescribed morphine.\textsuperscript{13} No difference in MEI was observed. It is likely that opioid-naive patients may have similar responses, regardless of the pain mechanism, although this aspect reserves further analysis, with better refinement of neurological examination and design specifically focusing on this subject.

Recent studies have assessed the use of so-called “strong” opioids in opioid-naive patients, an approach that essentially bypasses the second step drugs. Starting doses of 0.6 mg/day of fentanyl have been used successfully.\textsuperscript{14--16} Similar findings were found even in tolerant patients who were receiving 280--360 mg of codeine.\textsuperscript{17} According to this information, it could be concluded that doses of 0.6 mg/day would be universal, regardless of the previous treatment. This would suggest that an equivalent dose of 60 mg/day of oral morphine, which is a considerable dosage for opioid-naive patients, would be appropriate for all patients. This is unlikely in the clinical setting due to the high risk of adverse effects in opioid-naive patients. Adverse effects, in turn, are likely to reduce patient compliance. This observation was confirmed in a study in which transdermal fentanyl at doses of 0.6 mg/day, equivalent to about 60 mg of oral morphine, was better tolerated in codeine-using patients than in opioid-naive patients, who stopped the treatment prematurely in 21% of cases.\textsuperscript{18}

In another study comparing oral morphine and transdermal fentanyl, a high percentage opioid-naive patients who started strong opioids (transdermal fentanyl 0.6 mg/day or oral morphine 60 mg/day) developed moderate-to-severe adverse effects. Of interest, only about half of the patients completed the 4-week period of observation.\textsuperscript{19} Similarly, opioid-naive patients receiving 0.6 mg/day of transdermal fentanyl developed relevant adverse effects in comparison with patients previously treated with opioids for moderate pain or strong opioids, and were more likely to withdraw because of adverse effects.\textsuperscript{20} More interestingly, patients who started equivalent doses, morphine 60 mg/day, developed some adverse effects and titration was delayed in about 25% of patients, despite being relatively opioid tolerant, as they were receiving codeine or dextropropoxyphene.\textsuperscript{21}

The sequential treatment proposed by WHO has been compared with a direct administration of a strong opioid as a first step. Treatments appeared equally effective, although the group treated with opioids first had better pain relief and patient satisfaction, and a fewer number of therapeutic interventions. However, nausea was more frequently reported. Only 50% of patients in a control group needed strong opioids in doses similar to those used in patients who received strong opioids.
Unfortunately, the initial doses of strong opioids were not mentioned, making evaluation of data difficult. A similar approach has been recently proposed, showing that strong opioids may provide advantage over the traditional strategy in terms of the percentage of days with worst pain, but also require careful management of side effects. According to these data, it is likely that the doses of 60 mg oral morphine equivalents in opioid-naive patients, that is nontolerant patients, produce more consistent adverse effects. It seems to be obvious that the choice of the initial doses of morphine, not only the class of the drug, makes the difference in terms of compliance, efficacy, and tolerability. Thus, doses of morphine, or other strong opioids, should be as flexible and low as those in the range commonly used of opioids for moderate pain. In a previous study, even initial doses of 20 mg/day of morphine (the minimal dose available at that time) induced more adverse effects than dextropropoxyphene titrated for clinical use.

It is likely that a better response to morphine would have resulted from lower doses, as reported in the present study, reflecting the need for a slower titration in opioid-naive patients. The treatment was well tolerated even by older patients, who could be effectively titrated reporting similar effects to those found in younger adults, using lower doses of morphine. The number of dropouts was acceptable, considering the need to change opioids commonly observed in the cancer population due to an unfavorable response to morphine. The mean dose of morphine needed to maintain acceptable pain relief and tolerable adverse effects 1 week after starting the treatment was 30 mg, that is half the dose commonly prescribed in previous studies with the aim of skipping the second step. Mean doses of less than 45 mg/day of morphine were achieved 4 weeks after starting the low doses, which means that initiating with 60 mg/day would have resulted in overdosing. Initial higher doses, equivalent to about 60 mg of oral morphine equivalents, such as those proposed in the previous studies, would have been likely to be associated with adverse effects, and unnecessarily high opioid doses, which theoretically could mean a higher likelihood of tolerance. In a study of opioid-naive patients, the maximum doses reached after 4 weeks were 1.5 mg/day of transdermal fentanyl or 105 mg/day of oral morphine. Of interest, in previous studies the second step lasted about 3 weeks, before requiring strong opioids, assuming that the equivalent dose range of Step 2 opioids should be effective for a certain period in opioid-naive patients.

Thus, it seems clear that individualization of the treatment still remains the best method. In opioid-naive patients, opioid titration would start at the lowest level, as many patients may have a good response with minimal doses of morphine. From the data in this study, starting with low and flexible doses of morphine is the key, rather than use of a drug conventionally selected for the second step of the analgesic ladder.

Furthermore, in these last years, costs are of paramount importance all over the world, regardless of the type of health care system or insurance, both in developed and developing countries. The use of very low doses of morphine is very cheap in comparison with the use of opioids commonly used for moderate pain.

The WHO method should be still encouraged when approaching advanced cancer patients with pain. This method is associated with a high chance of success, despite the lack of the evidence needed to produce unbiased estimates of the proportion of patients for whom the ladder produces satisfactory results. However, it requires further refinements, and the approach used in this study could notably simplify the analgesic ladder, and also results in saving money. As morphine is the most available drug, other than being cheap, early use could be encouraged.

This study has obvious limitations, as in most studies of cancer pain, due to its open and uncontrolled design. However, the intent was exploratory, and has suggested that an alternative approach to the second rung of the ladder is feasible. The strength of these data should be challenged by controlled studies.

References


