Original Article

Low Morphine Doses in Opioid-Naive Cancer Patients with Pain

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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.

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).[1] 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

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due to the reluctance of health care professionals, institutions, and governments to use opioids because of fears of addiction, tolerance, and illegal use.[2] 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,[3–5] 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.[6]

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.[7] 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.[8,9] 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.[10]
- 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