Original Article

Efficacy, Safety, and Steady-State Pharmacokinetics of Once-A-Day Controlled-Release Morphine (MS Contin XL®) in Cancer Pain

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Abstract
The efficacy, safety, and pharmacokinetics of a novel once-daily morphine formulation (OAD morphine) and a 12-hourly formulation (twice-daily CR morphine) were compared in a double-blind, multi-centered crossover study. Chronic cancer pain patients (n = 25) were randomized to OAD morphine (mean 238 ± 319 mg q24h) or twice-daily CR morphine (mean 119 ± 159 mg q12h) for one week. They then crossed over to the alternate drug, which also was taken for one week. There was no difference between treatments for evaluations of overall pain intensity, analgesic efficacy, or adverse events. However, whereas pain scores increased during the day on twice-daily CR morphine (P = 0.0108), they remained stable on OAD morphine. Most patients (68%) chose once-daily dosing for continuing pain management (P = 0.015). The AUC ratio was 100.3%, indicating equivalent absorption. Fluctuation indices were 93.5 ± 28.8% and 179.3 ± 41.3% (P = 0.0001) for OAD morphine and twice-daily CR morphine, respectively. OAD morphine provides analgesia similar to twice-daily CR morphine with reduced fluctuation in plasma morphine concentration and more stable pain control. J Pain Symptom Manage 2005;29:80–90.

Key Words
Morphine, once-daily, controlled-release, clinical efficacy, cancer pain, pharmacokinetics

Introduction

The goal of chronic, analgesic therapy is to achieve continuous suppression of pain. This requires administration of analgesics on a regular basis, the next dose being given before the effects of the previous dose have worn off. Such a program can erase the memory and fear of pain, as well as reduce anxieties associated with its anticipated return.[1] Oral morphine has been described as an appropriate first choice for management of severe cancer pain.[2,3] Immediate-release morphine is generally administered every 3–4 hours, which may interrupt

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sleep and lead to non-compliance. Oral or transdermal opioid products that have sustained delivery properties offer round-the-clock pain relief with less inconvenience to the patient. Available oral controlled-release formulations are designed to maintain effective plasma morphine levels throughout a 12-hour dose interval and have been shown to provide effective analgesia during chronic oral administration.[4,5] The 12-hourly dosing regimen is beneficial in terms of reduced frequency with which plasma morphine concentrations fluctuate—a feature that may be clinically important in determining the extent of pain relief and incidence or severity of adverse events.

Although twice-a-day administration of oral morphine represents a significant therapeutic advantage over 4-hourly immediate-release morphine, a further reduction in dosing frequency should provide less fluctuation in plasma concentrations at steady-state, along with greater patient convenience and compliance.[6] Compliance improves as dosing frequency is reduced and an important action that health care providers can take to improve compliance is to select medications that permit the lowest dose frequency possible.[7] Therefore, a once-daily morphine formulation that offers acceptable pain control is likely to enhance compliance and ensure optimal effectiveness of treatment.

A number of oral sustained-release formulations of morphine have been developed with significant differences in their pharmacokinetics and bioavailability after single dose or steady-state administration. In clinical studies with other formulations, differences in pharmacokinetic variables such as fluctuation in plasma morphine concentration and time to maximum concentration have not been shown to translate into differences in extent of pain relief or the incidence or severity of adverse effects between 12- and 24-hourly formulations.[8–11] However, the decreased fluctuation in plasma concentration of longer-acting opioids may indeed provide more stable levels of pain control than their shorter-acting counterparts. Other controlled-released formulations, using transdermal delivery of opioids such as fentanyl, also have the potential to produce more stable plasma levels. Although transdermal fentanyl is usually effective in patients with severe cancer pain and can be of particular value for patients who cannot tolerate oral medication, oral administration is relatively inexpensive and easy to titrate and there are several alternative long-acting oral opioid formulations available.

Purdue Pharma has developed a once-a-day controlled-release morphine (OAD morphine) formulation with pharmacokinetic characteristics consistent with a 24-hour duration of action. In a single-dose bioavailability comparison with twice-daily controlled-release morphine (CR morphine), OAD morphine provided a comparable extent of absorption and a significantly reduced rate of absorption.[12] In a steady-state comparison with twice-daily morphine, the OAD formulation was characterized by a comparable extent of absorption and a significantly reduced fluctuation in plasma morphine concentration at the same total daily dose.[13]

The potential clinical advantages of OAD morphine over twice-daily CR morphine include an extended duration of action, reduced dosing frequency, increased compliance and possibly, more stable clinical effects, and fewer side effects as a result of less fluctuation in plasma morphine concentration. The objective of this study was therefore to compare the clinical efficacy, safety, and steady-state pharmacokinetics of OAD morphine and twice-daily CR morphine in cancer patients with chronic pain.

Methods

Subjects

Twenty-nine patients with chronic cancer pain and stable analgesic requirements were selected for participation. Stable analgesia was defined as that which required the administration of two or less rescue doses of opioid analgesic per 24-hour period, calculated as an average over three or more days. Patients were excluded from the study if they had intractable nausea or vomiting, a true allergy or intolerance to opioids, unstable renal function, were undergoing therapeutic procedures likely to influence pain during the study period, had a medical condition likely to interfere with drug absorption in the gastrointestinal tract, or if they were expected to use other opioid analgesics during the study. The study protocol and informed consent form were reviewed and approved by a research ethics board at each center, and all subjects gave written informed consent before participating in the study.