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Review TDD

Morphine: A Pharmacological Perspective on Its Cancer Pain Management

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Abstract

Morphine continues to be a key treatment in managing cancer pain because of its strong pain-relieving effects and established clinical history. Despite the emergence of alternative opioids and pain management therapies, morphine continues to be widely prescribed, particularly in palliative care settings. However, its use has been accompanied by concerns regarding tolerance, dependence, and adverse effects, which complicate long-term administration. This review explores the pharmacological aspects of morphine in cancer pain management, including its pharmacokinetics, mechanism of action, and the challenges it poses for patients. Special attention is given to pediatrics, geriatrics, and patients with renal or liver impairment. The article also discusses emerging therapeutic strategies, such as transdermal delivery systems, multimodal analgesia, and personalized medicine approaches, to improve pain control while minimizing side effects. Future research avenues and potential innovations in opioid therapies, including kappa and delta receptor agonists, provide promising directions to address the global challenge of cancer pain relief.

Keywords: Cancer pain management, morphine, opioid analgesics, opioid delivery, papaver somniferum

INTRODUCTION

Morphine has been used for centuries to relieve pain in cancer patients, in one form or another. International development work, coordinated by the World Health Organization, created a global health policy document for proper cancer pain management "Cancer Pain Relief", in which morphine occupied a central place. Global awareness of the benefits of morphine for cancer pain control increased because of the publication of this document, although the practice of regular administration of morphine advocated in the United Kingdom's first hospices took time to be established in other health care settings. Apprehension over the potential for tolerance and abuse of morphine lay at the heart of this slower uptake. Concerns about the use of morphine relieves pain related to cancer, which is widespread on a global scale, they also appeared on a micro level. Anxiety concerns are common among patients, health professionals, and caregivers, despite research showing the effectiveness of morphine as an analgesic. Many of them are rooted and representative symbolic or social meanings that are disconnected from clinical efficacy. The practical manifestation is that morphine can be prescribed suboptimal, not recommended at all, or diets are not respected by patients. The result is poorer symptom control. Although many new, potent synthetic opioids have emerged over the past century, morphine remains the most widely used opioid. In the world, because of a more liberal approach to pain medication [1, 2].

Opioids, especially in cancer patients and, more recently, also in patients with chronic non-malignant pain, the consumption of opioids is

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increasing. Morphine is no longer used only for short-term pain relief, such as in post-operative pain conditions and during the last hours of a dying patient, new problems and questions about its effect and mode of action during long-term use. The purpose of this study was to examine a possible correlation between pharmacokinetic and pharmacodynamic results (analgesia and adverse effects), evaluating blood samples from patients with chronic cancer during rapid- release M sulfate oral titration phase (ORAMORPH: Molteni Pharmaceutica, Scandicci, Florence, Italy). Possible relationship between doses at the end of titration phase (when pain relief is achieved), negative effects and the plasma concentration of M and the main metabolites of the drug, glucuronides M3 and M6, were considered. The administration of morphine in cancer patients has proved that in addition to the analgesic effect, morphine can significantly modify tumor growth [3].

Over the past decade, numerous studies have been carried out using cancer cell lines and animal models to explore the complex mechanisms by which morphine influences tumor cells. Although the pharmacology and function of opioids in the central nervous system are well understood, their impact on cancer cells remains largely unknown. The results so far are contradictory. In the past, Morphine has been reported to increase endothelial cell proliferation tumors. Conversely, morphine and other opioids have been shown to induce tumor cell death. Several studies have explored this topic from various angles, with this review concentrating on recent findings regarding morphine's impact on tumor cell proliferation, apoptosis, angiogenesis, and migration. Surveys and observational studies have shown that many patients suffer from bothersome or severe pain and do not receive adequate pain relief. Also, although the literature confirms the effectiveness of most opiate/opioid drugs for treatment of chronic pain, information on dose titration is limited, there is no definitive data in relation to the clinical indications in this context, neither their potential clinical/pharmacological predictors its effectiveness or negative effects (Figures 1–2).

In fact, heterogeneity is the complexity of different types of cancer, individual sensitivity to pain, as well as history, sex, age and genetic polymorphisms of patients prevent the development of standardized classification and uniformity of therapeutic processes [4, 5].

Figure 1. Papaver Somniferum Plant.

Morphine

The specific arrangement of these atoms is crucial for their pharmacological activity.

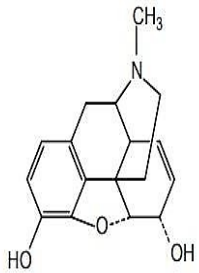

Figure 2. Chemical Structure of Morphine.

Chemical formula: $C_{17}H_{19}NO_3$; Molecular weight: 285.34 g / mole.

Mechanism of Action

Morphine exerts its analgesic effects mainly by binding to mu-opioid receptors located in the brain, spinal cord and peripheral tissues. This link results in:

Administration of Morphine

- Binding to opioid receptors (mainly mu receptors in the CNS).
- Inhibition of transmission of pain signals (Decreased release of neurotransmitters, such as substance P).

Activation of Descending Inhibitory Pathways

(Improving the suppression of pain signals)

- Altered pain perception (Reduces pain intensity and improves comfort).
- Emotional and psychological relief (Reduces anxiety and fear associated with pain).
- Improve the quality of life (Facilitates better engagement in daily activities).

PHARMACOKINETICS

Absorption

After oral administration, morphine is primarily absorbed in the alkaline environment of the upper small intestine (since morphine is a weak base), with nearly complete absorption.

Morphine is also well absorbed across the rectal mucosa. Buccal absorption of oral morphine solutions seems effective, but tablet formulations have shown poor and inconsistent absorption through this route. Likewise, the absorption of inhaled morphine appears to be inadequate [6].

Distribution

Morphine is highly lipophilic, which allows it to be distributed quickly in the body. The volume of distribution typically ranges from 2 to 4 L/kg. This broad distribution is affected by factors, such as age, body mass index, and conditions that impact tissue perfusion.

Blood-Brain Barrier

Morphine effectively crosses the blood brain barrier, where it exerts its central analgesic effects. This insight is essential for its effectiveness in the treatment of severe pain [7–10].

Metabolism

Only a minor fraction of the morphine absorbed after oral administration reaches the systemic circulation. Because of significant first-pass metabolism, the bioavailability is low and inconsistent. Mean values have been reported to vary between 19% and 47%. 4 percent of a dose of morphine is excreted as the nor-morphine and its glucuronide metabolites. The remaining part can be explained by excretion through other ways (for example, feces and sweat).

Excretions

The prominent role of the kidney in the excretion process of morphine metabolites has been demonstrated in a study of patients with renal failure given intravenous (IV) morphine. Subsequent plasma concentrations of M3G and M6G were Observed to be several-fold greater in these patients than in a control group with normal renal function. When kidney transplantation was performed in patients with renal impairment, the metabolite accumulation was abolished [11–13].

Special Patients Populations of Cancer

Pediatric Patients

Pediatric cancer patients present unique challenges in pain management due to various developmental and pharmacokinetic factors.

Example: Infants, children, toddlers etc.

Dosage Considerations

The pediatric dose is usually calculated based on body weight or body surface area, often starting from 0.1 to 0.2 mg/kg for oral administration, adjusted based on response continuous infusion can be used for severe pain management, with careful monitoring required to adjust doses appropriately.

Side Effects

Common side effects include constipation, sedation and possible neurotoxicity, especially if doses are not managed correctly.

Pharmacokinetics

Oral and subcutaneous routes are commonly preferred because they are easier to use and carry lower risks compared to intravenous administration.

Geriacticpatients

The elderly population presents particular pharmacological considerations due to age-related physiological changes.

Example: old age patients.

Pharmacokinetic

Age-related changes in liver and kidney function can greatly impact the metabolism and elimination of morphine.

Start with lower doses (e.g. 2.5–5 mg orally) and slowly increase based on clinical response.

Cognitive Impairment

Geriatric patients may have comorbidities or cognitive impairments that complicate pain management. Monitoring sedation and confusion is essential.

Polypharmacy

Older adults often take multiple medications, which increases the risk of drug interactions. A careful review of all medications is necessary to avoid side effects. 3. Patients with renal failure renal dysfunction significantly affect the pharmacokinetics of morphine due to the accumulation of metabolites, especially M3G.

Patients with Liver Failure

- Liver function is essential for the metabolism of morphine.
- Liver failure can cause the accumulation of morphine and its active metabolite, M6G.

Doing Strategies

Start treatment with lower doses (5 to 10 mg) and increase the dose carefully. Ongoing monitoring is crucial to prevent adverse effects from the buildup of metabolites.

Adverse effects of morphine- although morphine is effective, its side effects can be significant:

Constipations

The most common side effect, which requires preventive measures, such as laxatives.

- *Nausea and Vomiting:* It can typically be controlled with antiemetics, though some patients may develop tolerance over time.
- *Respiratory Depression:* A potentially life-threatening condition, especially in opioid-naïve

patients or when doses are rapidly increased. Sedation: May impair cognitive function and increase the risk of falls, especially in adults.

- *Dependence:* Long-term use can lead to physical dependence, which requires careful management and monitoring.
- *Hormonal Effects:* Opioid-induced hypogonadism can occur, affecting quality of life.
- *Tolerance:* Over time, patients may require higher doses to maintain the same level of pain relief.
- *Withdrawal Symptoms:* Stopping suddenly can lead to withdrawal, including anxiety, insomnia and gastrointestinal upset.

Challenges in Cancer Pain

Palliative care aims to prevent and alleviate patient suffering through early identification and accurate assessment of pain and other symptoms, meaning morphine should not be limited to terminal cases. The medication can be given by adjusting the dose to manage symptoms effectively. This highlights the importance of making pain-relieving medications available in healthcare facilities to ease the pain of patients at any stage of cancer. In Ethiopia, morphine is listed as an essential medication. Oral morphine is used in country hospitals and some cancer centers to relieve pain caused by this chronic disease. However, nearly all healthcare services offering cancer care have consistently reported a shortage of this drug. Intermittent supply of this drug from public and private suppliers has been observed at various times, but the supply is very irregular with extended periods of shortage/lack of stock. The primary challenge to local morphine production has been the absence of this drug in the domestic market. Despite efforts to improve availability through imports from other countries, such as 30 mg tablets, these supplies have proven insufficient to meet the growing demand. Additionally, the imported product did not meet the dosage requirements or convenience for pediatric patients. Cancer-care centers are currently facing shortages of this medication. While regional institutions like Hospice Africa Uganda continue to provide technical assistance and share best practices, the issue of oral morphine availability remains unresolved. The country has implemented various policies and structural measures, but more needs to be done to address the cancer burden. Ensuring proper care for cancer patients is one of the key areas to focus on to alleviate their suffering.

Future Approaches in Cancer Pain Management

Improved Transdermal Administration System

Transdermal patches provide sustained release and stable plasma levels, improve compliance and comfort.

Example: Duragesic, morphbond, fentanyl etc.

Intrathecal Administration

Direct Delivery

Direct delivery to the spine can provide potent analgesia with reduced systemic side effects.

Example: Morphine sulfate injection, flumorph, delomorphic etc.

Combined Therapies

Multimodel Analgesia

Combining morphine with NSAIDs, acetaminophen, or additional medications (e.g., antidepressants, anticonvulsants) can improve analgesia and reduce opioid dependence.

Synergistic Effects

Mechanisms of Action

The use of medications with different mechanisms can provide better pain control with lower doses of morphine.

Adjunctive Medications

The combination of morphine with additional analgesics, such as gabapentinoids, antidepressants, or corticosteroids can improve pain control. These medications can affect various pain pathways, possibly enabling the use of smaller morphine doses.

Emerging Therapie

Research into cannabinoids and other new pain relievers may complement morphine in future treatment regimens, providing alternative mechanisms of action and additional benefits.

New Opioids and Analogues

- *Kappa Opioid Receptor Agonists:* Study of compounds that target kappa receptors may provide analgesia with a lower risk of addiction.
- *Centrally Acting Kappa Agonists:* Drugs, such as CR845 (difelikefalin) are selective kappa opioid receptor agonists that can provide potent analgesia with a significantly reduced risk of respiratory depression and euphoria. Kappa agonists may also have a lower addiction potential than traditional opioids.
- *Cancer Pain Management:* Kappa agonists emerge as potential adjuncts in the treatment of cancer pain, particularly in cases of advanced pain or when opioid tolerance develops.

Delta Opioid Receptor Agonists

- *Deltorphin Analog:* Research on delta opioid receptor agonists, such as deltorphin analogs, is promising. These compounds have demonstrated strong pain-relieving effects while presenting a reduced risk of respiratory depression.
- *Cancer Pain Management:* Delta opioid receptor agonists may provide a new avenue for treating chronic cancer pain, particularly in opioid-tolerant patients or those with side effects from standard opioids.

Biological Products and Gene Therapy

- *Emerging Therapies:* Research into gene therapies targeting specific pain pathways shows promise for more effective cancer pain management.

Non-Opioid Analgesics with Opioid-Like Effects

- *Agonists of the TRPV1 Receptor:* These receptors, located on the fibers of the pain- sensing nerve, are involved in the sensation of heat and pain. Agonists targeting TRPV1 receptors can alleviate pain without the typical side effects linked to opioids.
- *Cancer Pain Management:* TRPV1 agonists are still being studied, but they can be used in combination with opioids or as stand-alone treatments for patients with refractory cancer pain.

Personalized Pain Management

Pharmacogenomics

Understanding genetic variations in drug metabolism can help adapt morphine treatment to each patient, optimizing efficacy and minimizing side effects.

Biomarker

Identifying biomarkers associated with cancer pain and response to morphine may lead to more personalized treatment plans. Biomarkers can indicate not only pain levels but also the predicted response to opioids, guiding clinicians to choose the most appropriate pain management strategy.

Patient-Centered Approaches

Integrating patient preferences, pain history, and psychological factors can lead to more effective pain management strategies. This may include the use of morphine in combination with non-opioid medications or adjunctive therapies (such as cognitive behavioral therapy) tailored to the individual's needs.

Doing Strategies

Using advanced algorithms and machine learning to analyze data from large patient populations can help develop dynamic dosing regimens. These regimens allow the dose of morphine to be adjusted in real time based on patient responses and pain levels, ensuring optimal pain control.

Patient Educations and Engagement

Improving patient understanding of pain management strategies and the role of opioids can improve treatment adherence and satisfaction.

Comprehensive Information Sharing

Patients will receive comprehensive information about morphine, including its mechanism of action, potential side effects, and the importance of following prescribed treatment regimens. Educational materials will be tailored to everyone's level of understanding, possibly incorporating multimedia resources (videos, apps).

Use of Technology

Digital platforms will facilitate continuous education and communication. Applications can provide information on morphine dosage, monitor pain levels, and provide reminders about adherence to treatment.

Continuing Education

Ongoing education is essential as treatment progresses. Regular checkups can help inform patients about new findings about morphine use, emerging alternatives, and developing pain management techniques.

Precision Medicine

Advances in genomics may lead to personalized pain management strategies, tailoring opioid use to individual genetic profiles and responses.

Genomic Profiling

Understanding genetic variations can help identify how patients metabolize morphine and respond to pain relief. Genetic testing can guide opioid dosing and selection.

Pharmacogenomics

Studying how patients' genetic makeup affects their response to morphine can lead to personalized dosing strategies, reducing the risk of side effects and improving pain management.

Manage Comorbidities

Understanding and managing comorbidities (such as anxiety or depression) that affect pain perception can improve overall pain management strategies.

CONCLUSIONS

Morphine remains a cornerstone of cancer pain management due to its powerful analgesic properties and well-established role in clinical practice. Comprehending its pharmacological characteristics, determining suitable dosing approaches, and effectively managing side effects are crucial for enhancing patient outcomes. Ongoing research into pain mechanisms and alternative therapies continues to refine our approach to cancer pain management, ensuring that patients receive effective and compassionate care.

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