

Use of opioids in the management of oncological pain

Uso de opioides en el tratamiento del dolor oncológico

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 **Citar como:** Benitez Rojas LC, Benitez Rojas A, Rojas Perez SC. Use of opioids in the management of oncological pain. Inmedsur [Internet]. 2020 [cited: date of access]; 3(1): 82-89. Disponible en: <http://www.inmedsur.cfg.sld.cu/index.php/inmedsur/article/view/66>

 **ARTÍCULO DE REVISIÓN**
Sección "Shakespeare"

ABSTRACT

An updated literature review was made using the resources available in Infomed, specifically Ebsco and PubMed, and from MEDLINE database with the aim of describing updated aspects of oncological pain management using opioid medications. Of the total bibliography consulted, 35 were cited in the work, using qualitative research methods. It was concluded that opioids, especially morphine, are the drugs of choice in these cases. Most of the literature consulted refers that the management of cancer pain is inadequate due to insufficient knowledge of health professionals about their evaluation and strategies to reduce tolerance, physical dependence, opioid addiction influences the negative attitudes of patients, and family members and the inconveniences related to regulations for the control of these drugs and their adverse effects.

Key words: morphine; cancer pain; analgesics; opioid; opioid rotation

RESUMEN

Se realizó una revisión bibliográfica actualizada a través de los recursos disponibles en Infomed, específicamente Ebsco y PubMed, y de la base de datos MEDLINE, con el objetivo de describir aspectos actualizados del manejo del dolor oncológico utilizando medicamentos opioides. Del total de la bibliografía consultada, 35 fueron citadas en el trabajo, se emplearon métodos de investigación cualitativos. Se concluyó que los opioides, especialmente la morfina, son los fármacos de elección en estos casos. La mayor parte de la literatura consultada se refiere a que el manejo del dolor por cáncer es inadecuado debido al conocimiento insuficiente de los profesionales de la salud sobre su evaluación y estrategias para reducir la tolerancia, la dependencia física, la adicción a los opiáceos influye en las actitudes negativas de los pacientes y los miembros de la familia y los inconvenientes relacionados con Regulaciones para el control de estas drogas y sus efectos adversos.

Palabras clave: morfina; dolor en cáncer; analgésicos opioides

INTRODUCCIÓN

Cancer is the second leading cause of death worldwide, and was responsible for 8.8 million deaths in 2015. Population studies indicate that the number of new cases is likely to increase by 70% in the coming decades, reaching 24 million cases approximately in the year 2035.^{1,2} The World Health Organization (WHO) estimates that the overall survival rate in patients treated for cancer at 5-year term exceeds 50% in developed countries. In developing countries, the 5-year survival rate is less than 30% and in Latin America and the Caribbean, this figure estimate at around 40% of the cases.³

In Cuba, in 2018, cancer was the second cause of death with a rate of 221.3 per 100,000 inhabitants, preceded only by heart diseases. The mortality rate by type of cancer higher in both sexes corresponds to the malignant tumors of the trachea, bronchi and lung.⁴

The pain suffered by patients with this disease is a reality of great magnitude. It appears in 40% in the initial and intermediate stages of cancer, up to 70-90 % in advanced stages and it is related to the progression of the disease, causing a great impact on the quality of life of these patients.^{5,6}

Although, the pathophysiological mechanisms responsible for chronic pain are complex and are in permanent study, it is possible to describe the bases of pain feelings.^{7,8} Pain management is a frequent challenge in medical practice. Unlike acute, chronic control can be difficult to achieve, either in patients with or without cancer.⁹

There are multiple measures to manage pain caused by cancer, which range from pharmacological medication, psychological therapies and surgical measures as options for each patient. Since it always has to be evaluated individually and know what type of pain is faced and therefore provide the best therapeutic option¹⁰ this clinical decisions are usually averaged among diverse priorities such as promoting health, saving resources, relating cost-benefit and developing health-friendly lifestyles and patterns.¹¹

One of the conflicts that medicine faces in society is the attention to terminally ill patients, which gets reached when the disease does not respond to specific treatments established to cure or stabilize it. This leads to death in a variable time (generally less than six months), and the process

is characterized by causing, in general, a high degree of physical, psychological and family suffering.^{12,13}

Since 1986, WHO has been promoting a protocol as a reference framework for the use of analgesics in oncological pain, based on the use of treatment steps in a staggered manner. The intensity of the pain determines the step at which treatment should be started, and the lack of pain control indicates the need to associate another analgesic or to move on to the next step.¹⁴

The first step considers the use of non-opioid analgesics to treat mild pain; whereas, the second step recommends weak or minor opioid analgesics, associating in case of need non-opioid analgesics, for moderate pain; finally, the third step considers the use of potent or greater opioids, with or without non-opioid analgesics.¹⁴

It has been commented that the cornerstone for cancer pain control are powerful opioids, in particular morphine sulfate, because it has no "ceiling" effect and when increasing the dose, it increases its power in a semi linear way until the desired analgesia is obtained or presenting adverse effects.^{5,15}

WHO considers the prescription of opioid analgesics in a country as an adequate indicator of the way pain is treated.^{16,17} Despite this, this organization has recognized a broad set of structural obstacles that prevent millions of cancer patients from gaining access to opioids and the treatment of specialized health professionals.

Among these factors are the regulatory or regulatory obstacles, the attitude towards the use of opioids by medical personnel.¹⁴ In addition to this it is suggested that there are barriers related to the patient and their direct environment given by the fear of becoming addicted to analgesics, believing that the side effects will be worse than pain, the hopelessness of being able to control pain, associating pain with progression of illness, fear that powerful analgesics are injectable, among others.¹⁸

Therefore, in order to obtain good results, healthcare professionals must act on all fronts, emphasizing better training of professionals linked to both direct patient care and those involved in the care of families and caregivers such as general practitioners, social workers, psychologists, etc.

The topic has generated very diverse opinions within the

international medical community. There are those who show a perspective of rejecting its use, giving rise to the so-called "opiophobia", that is, the fear of using opioid drugs. In most cases, by the myths that persecute the derivatives of opium, associated with ignorance of its systemic effects.¹⁹

In Cuba there seems to be a deficit in the use and prescription of opioid analgesics to achieve adequate pain control in patients with cancer. In an article published in 2016 in the Cuban Journal of Pharmacy entitled Prescription of morphine in patients treated at the Institute of Oncology and Radiobiology it was found that the indication of morphine was inadequate in 1.6 % and partially adequate in 13.5 %, the therapeutic scheme was inadequate in 17.8 % of the patients, while the individualization of the treatment and drug combinations were inadequate in 32.9 % and 12.6 % respectively.²⁰

On this subject, Dr. Isabel Martínez Peñalver, Director of the Cuban Journal of Oncology, has stated that there is resistance to the use of this product, not because of ignorance of its effects in relation to pain, but because of the fear of addiction, as well as the complexity of the bureaucratic mechanisms that control their use.²¹

The pain relief is linked to the quality of care of the oncological patient and the doctor has the ethical duty and the moral obligation to it, with the available resources and with adequate knowledge. When fulfilling the ethical duty to alleviate pain, not only life is dignified, but also death, a good medical practice is that directed to achieve adequate objectives, based on the promotion of the dignity and quality of life of the patient.²²

Among the ethical dilemmas faced are the decision to initiate treatment, the time at which it should be initiated and the drugs to be used, especially the use of opioid drugs for this type of pain, as well as the choice of route of administration of opioids and the professional ability to adequately manage the painful syndrome.⁶

Because of this, there is a need to update the scientific community on aspects related to the management of oncological pain, looking specifically at the prescription of opioid drugs and all the dilemmas that may arise due to their beneficial and adverse effects on the patient's health. This is the main motivation of the present revision, with the aim of increase the knowledge in the students of the

careers of the medical sciences and professionals of this branch in this subject.

DEVELOPMENT

Physiopathology of cancer pain

Pain in general is defined as "an unpleasant sensation and an emotional experience associated with a current or potential tissue damage," according to the International Association for the Study of Pain.^{7,23}

Thus, an acute and high intensity stimulus, related to tissue injury, produces the activation of afferent circuits generating a state of algesia that, after a progressive development, usually resolves in days or weeks parallel to sensory healing. However, this resolution of the tissue injury may not result in a resolution of the pain state, producing a persistent inflammation with nerve injury, which leads to permanent changes in nerve function and a state of persistent chronic pain.⁷

There are two types of pain receptors or nociceptors: those that respond to thermal and mechanical stimuli and rapidly transmit the signal through myelinated fibers (A δ) and those that are connected to unmyelinated fibers (C), slower conduction, They respond to pressure, temperature and other types of stimulation.²³ For the specific cases of pain in cancer patients, some author describes that at the cellular level, the tumor cells release prostaglandins, cytokines and growth factors that attract inflammatory cells and activate these nociceptors. If the tumor is rapidly growing, nerves are compressed or get injured by hypoperfusion or direct proteolysis. In the case of bone metastases, they release of prostaglandins, bradykinin, substance P and histamine together with the occupation of space by the tumor and the pressure exerted on the periosteum. On the other hand, the increase in osteoclastic activity generates pH decrease, with the activation of nociceptors sensitive to these changes.¹⁸

The sensation of pain then occurs due to the activation of a constellation of brain regions by these nociceptive stimuli, affected also by various emotional states and behaviors. Through a neural hierarchical network the coding of the nociceptive stimulus, the conscious modulation of pain and the formation of memory of pain progressively takes place.⁷

For the reasons explained above, it is correct to state that a patient with cancer suffers from pain at some point during the course of their illness, and regardless of what causes it, it must be treated to alleviate their suffering. The pharmacological treatment must be instituted from the beginning of the irruption of the pain and it is maintained through the diagnosis, evolution and until the end of the life of the oncological patient.

WHO Analgesic Ladder

In 1986, the WHO (World Health Organization) proposed a reductionist model of cancer pain management consisting of three consecutive steps, the so-called WHO Analgesic Ladder.¹⁴ This method is effective in alleviating pain in approximately 90% of cancer patients and in more than 75 % of terminal cancer patients.¹⁸

The first step of this ladder is for mild pain, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are used, without evidence of efficacy differences and analgesic coverage. Acetylsalicylic acid, ibuprofen and diclofenac are considered to be of choice to treat mild pain caused by bone metastases. In the case of moderate pain (second step) it is recommended to use weak or minor opioids: codeine and tramadol and dihydrocodeine. These also present analgesic ceiling and are indicated to treat moderate pain that does not respond to NSAIDs.¹⁴

For severe pain the use of major or potent opioid analgesics is proposed. Due to its effectiveness, easy dosage and risk/benefit ratio, this is the most important class of analgesics in the management of moderate to severe oncological pain. Generally the most used in the world is Morphine, due to its availability in different forms of presentation, its well-defined clinical pharmacology and its relative low cost, but health personnel, patients and family members avoid its prescription or use out of fear to the supposed adverse effects it produces. Hence, most patients with cancer remain with pain of varying intensity despite the treatment imposed, because they are not provided with the analgesics they need or is done inadequately and insufficiently.⁶

Therefore it is necessary to explain the mechanisms by which these drugs act to understand their effects on the body and thus be able to notice its advantages and disadvantages.

Mechanism of action of opioid drugs

Opioid drugs exert their analgesic effects predominantly through binding to mu or μ receptors. The μ receptors are densely concentrated in the regions of the brain that regulate the perception of pain, including emotional responses induced by pain and in the brain reward regions that intervene in the perception of pleasure and well-being. This explains why opioid medications can produce both analgesia and euphoria. The μ opioid receptors in other regions of the brain and peripheral organs represent other common effects of opioids.^{24,25}

The identification of the different morphine receptors has allowed to distinguish four types of opiate molecules (Mu, delta, kappa, sigma). Parallel to the analgesic effect (therapeutic effect) there is a state of euphoria, decrease anxiety, states of excitement and a hypnotic effect, central neurovegetative effects (respiratory depression, hypotension, bradycardia) and peripheral effects on the smooth muscle (constipation due to decreased peristalsis, bronchospasm, etc.)^{26,27,28}

When taking into account the obstacles that WHO indicates in the use of these substances, it is possible to observe that there are three main actors: the doctor, the patient and the regulatory authorities. The factors that include these three actors are diverse. From the lack of knowledge of the doctor and the patient, and wrong attitudes in relation to pain and the therapeutic use of opioids, to the existence of restrictive policies and legislations that regulate excessive control of medicines, the existence of barriers and failures in the system of acquisition and distribution of controlled drugs, the lack of coverage of opioid analgesics and, finally, the high cost of some analgesics for the treatment of pain.²⁰

Dilemmas in the prescription of opioids

One of the aspects to consider before starting the treatment with opioids are the risk factors related to their abuse, addiction and use for recreational purposes other than doctors. The potential for abuse and addiction to opioids derive from the cerebral reward mediated through the dopaminergic pathways that trigger those patients who show a biological predisposition. These patients who are treated with opioids for the relief of chronic pain may develop a disorder resulting from the abuse.⁶

The doctor, for his part, avoids prescribing opioids, or does

so in a limited way, for fear of the emergence of tolerance and physical dependence.

Tolerance and physical dependence

The repeated administration of any opioid, almost inevitably leads to the development of tolerance and physical dependence, events that differ and should not be confused with addiction. This predictable phenomenon reflects the counter adaptation between the receptors and their intracellular signaling cascade.²⁴

In addition, with repeated administration, tolerance leads to a decrease in opioid potency. Therefore, the prolonged prescription of opioids for their analgesic effects will normally require increasing doses, in order to maintain the initial level of analgesia up to 10 times the original dose. Similarly, tolerance to the rewarding effects of opioids leads to the progressive increase of doses, observed in opioid addiction, which can result in daily doses of up to 800 mg morphine equivalents (MME, factor conversion used to facilitate comparison of potency between opioids).²⁴

Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescription. Addiction occurs only in a small percentage of people exposed to opioids—even among those with pre-existing vulnerabilities²⁴ and that addiction involves both an aberrant use of the opioid and a maladaptive social behavior, although in the case that it has acquired addiction due to the medical use of the substance it is defined as pseudoaddiction.³⁰

Tolerance is a pharmacological property of opioids that defines the need for higher doses to maintain the analgesic effect, physical dependence is a physiological adaptive state between the opioid and its receptor according to the concentration of drug. This is characterized by the presence of abstinence after its abandonment and as a chronic neurobiological disorder.^{31,32,33}

As an addiction mitigation strategy, it is recommended to evaluate the risks of addiction before prescribing opiates. Emergent signs of addiction can be identified and managed through regular monitoring, including pharmacological analysis of urine before making each prescription, to assess the presence of other opiates or drugs of abuse. The responsible physicians must be prepared to make the referral to the specialist for the treatment of addiction, when indicated.²⁴

Another obstacle for which opioids are not prescribed in the correct way is the fact that they present a series of adverse reactions that instead of improving the patient's health state can bring complications to it.

Constipation

Constipation is the main long-term adverse reaction that can occur in a patient receiving opioid treatment and it is considered to be the main cause of the low prescription of these substances.

Constipation induced by opioids is an adverse effect for which tolerance does not develop. Its management includes a prophylactic treatment since hygienic-dietetic measures are not usually effective and reducing an effective dose of opioid does not constitute an adequate treatment to control pain. Therefore, in the Interdisciplinary Oncological Pain Surveys published by Yolanda Escobar Álvarez, in 2016 the use of opioids different from morphine is proposed with fewer gastrointestinal adverse effects, such as tapentadol marketed as Palexia®, with the same analgesic capacity as the other major opioids. In those cases in which constipation is established, the laxatives are the first therapeutic resource, in patients resistant to laxatives the option is PAMORA, of which one of the most used with proven effectiveness is naloxegol marketed as Moventing® and methylnaltrexone.³⁵

There are other deversive reactions that are also considered when making the decision to prescribe these medications such as respiratory depression, nausea and vomiting, hyperalgesia, opioid-induced endocrinopathy, opioid-induced immune changes among others that is also part of the causes of low prescription.³⁵

Opioid rotation and its importance

Sometimes the patient experiences side effects beyond those that can be controlled with simple measures and it is necessary to change the medication for another with its same effects. This change is opioid rotation and is part of the dilemmas towards the use of opioids. A change may be needed for logistical reasons, such as changing the route of administration (for example, from intravenous to oral, in preparation for discharge from the patient, or from oral to patches due to severe odynophagia). The need to minimize toxicity with the onset of hepatic or renal failure (eg, from morphine to fentanyl or methadone), and cost considerations (eg, long-acting oxycodone to methado-

ne).^{14,35}

The selection of an opioid depends on the reason for the rotation. All strong opioids have similar efficacy profiles and side effects in equianalgesic doses. Due to the lack of specific opioid predisposing factors, empirical trials are needed to identify the ideal opioid. If the opioid-induced neurotoxicity is the reason for the change, it may not matter which opioid changes, as long as it is a different drug. It is important to highlight that the patient's preference, the history of consumption of opioids, the route of administration and the cost are necessary considerations before making the final decision.³⁵

In an opioid rotation study in the ambulatory palliative care setting, it was revealed that approximately one third of the 385 consecutive patients needed opioid rotation, especially for uncontrolled pain (83 %) and opioid-induced neurotoxicity (12 %). The success rate was 65 %, with a median pain improvement of 2 points out of 10 (the clinically important minimum difference is 1 point).²⁸

So we can affirm that opioids rotation is a real and good therapeutic option for these type of treatment. In the case of the patient with cancer, the treatment of pain will always be a useful medical intervention, because the results will always favor the patient, regardless of the stage of his illness. The expected benefit will outweigh the risks that therapies may bring. Therefore, the treatment of pain should never be limited or rejected.

If the aim were to alleviate the pain, having exhausted other therapies that lack negative effects, there would be no ethical disadvantages in administering them, as long as the adverse effects are not directly sought, but only tolerated, as there are no other effective alternatives available. Under these conditions, the management of oncological pain would represent the greatest possible good for that patient.

CONCLUSIONS

Morphine is the medication of choice for the effective treatment of cancer pain, however it is consensus in the majority of the literature consulted that its prescription is inadequate, due to a large extent, to the insufficient knowledge of health professionals about its evaluation. The strategies to reduce the tolerance, physical dependence and addiction developed by patients treated with

opioids to alleviate pain, are described as other factors that cause the low prescription of this type of medication. Negative attitudes of patients and relatives, as well as the drawbacks related to the regulations for the control of these drugs and the control of their adverse effects are also factors to consider.

CONFLICT OF INTERESTS

The authors declare that does not exist conflict of interest.

AUTHORS CONTRUBUTION

All the authors participated in the writing, revision and approval of the article and its final version.

FINANCING

The authors did not received founding for the development of this review.

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Received: October 2nd, 2019

Accepted: November 4th, 2019

Published: April 13th, 2020



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