Under-use of opioids in oncological pain

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Abstract

Pain is a common problem that greatly affects the quality of life of oncological patients. Opioids, particularly morphine, are of great importance for treating pain, but the secondary role given to them in the teaching of medicine means they are often incorrectly used. Popular myths among patients, concerning oncological pain and analgesics, often makes them reluctant to report pain and adhere to the treatment.

It is of utmost importance to prescribe opioids appropriately and discuss with patients the need to use them, as well as their side effects, thereby avoiding unnecessary suffering for many of these patients.

Key words: opioids, morphine, oncological pain.

Introduction

Pain is one of the main factors that affects the quality of life of cancer patients, and for many, is more feared than death itself. If not properly treated, chronic pain can lead to other symptoms, including sleep disturbances, loss of appetite, decreased concentration, irritability and depression.[1] Between 30 and 50% of people with cancer suffer, or are treated for pain,[1] and this percentage increases to around 60 to 90% as the disease progresses.[2] Factors that can contribute to the onset and intensity of pain include the location of the primary tumor, and in particular, the presence of bone metastases, visceral involvement or involvement of the nerve by the tumor or by metastases, and anxiety and depression.[1] In around 25% of cases, the pain is caused by treatment (postoperative pain, neuropathic pain from vincristine, stomatitis from chemotherapy or radiotherapy, etc.), and in less than 10%, the pain is not related to the cancer (e.g. arthritis).[3] The majority of patients have pain in more than one location, generally caused by several of the factors mentioned above.

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One of the priorities of the World Health Organization (WHO) in its program for the fight against cancer is the fight against pain and other symptoms, along with the prevention of diagnosis, early diagnosis, curative treatments and the implementation of national programs in the fight against cancer. In 1986, the WHO published Traitement de la douleur cancéreuse (cancer pain management) introducing the "analgesic ladder" method:

The first step recommends the use of Paracetamol and aspirin, or other non-steroid anti-inflammatory drug (NSAID), to treat mild or moderate pain. The second step recommends the use of mild opioids, such as Codeine or Dextropropoxyphene, which are added to the drugs of the first step if the pain persists or increases (some commercial preparations exist in which these drugs are associated). If the pain is still not controlled, or if it is intense from the start, stronger opioids should be used, such as morphine, methadone, etc., which make up the third step, in which case the non-opioid analgesics of the second step may or may not be maintained. In any of the steps, an adjuvant or co-analgesic may also be associated (i.e. a drug without intrinsic analgesic activity but which in some situations may contribute to pain control), such as tricyclic antidepressants for neuropathic pain, or Carbamazepine for neuropathic pain with an excruciating component, corticosteroids, etc.[1] The WHO considers morphine the strong opioid of choice, and includes it in its list of essential drugs.

Various studies have shown that with this method, it is possible to control pain in the majority of patients.[1,4,5] However, it is calculated that in developed countries, the pain is not treated in around 50% of

patients,[1] and the main reason for this situation is the under-use of opioids.

Causes of under-use of opioids

Pain has been relegated to a secondary position in the teaching of oncology, which has led to an often incorrect or non-existent assessment and a lack of knowledge concerning the clinical pharmacological approach to its treatment.[2,6] Doctors, in general, do recognize the high prevalence of oncological pain, and the frequency with which it remains untreated.[7] Opioids are generally prescribed based on the habitual practice of other doctors, and not based on pharmacological knowledge, and the most common errors are over-evaluation of the duration of the action, and under-evaluation of the effective analgesic dose;[8] thus, prescription based on habitual practice leads to a perpetuation of these errors.[8] The public sees pain as a virtually constant symptom, and more intense than it actually is.[7] Many patients, because they believe that pain is an inevitable part of cancer, or through refusal to recognize that the disease is progressing, do not report pain spontaneously. Both doctors and patients share an excessive concern with drug addiction, tolerance, and the side effects of opioids, resulting in a reluctance to use them appropriately.

The fear of opioid-dependence, as mentioned above, is shared by both doctors and patients. Effectively, there are two types of dependence: physical and psychological. Physical dependence of the physiological neuroadaptation mechanism[8] leads to the appearance of physical symptoms resulting from the withdrawal or sudden suspension of an opioid that has been used regularly for some time. This is a common phenomenon, which is easy to predict and resolve through a gradual reduction in dose:[9] initially maintaining 25% of the habitual dose for 2 days, and then reducing it by 50% every 2 days, until a daily dose equivalent to 10 - 15 mg of morphine is reached, at which point it can be suspended; for example, in a patient taking 240 mg of morphine a day, whose pain has been controlled by an anesthetic technique, can immediately be put on 60 mg a day for 2 days, followed by 30 mg for another 2 days, and finally, 15 mg for another 2 days, at which point it can be suspended. Psychological dependence (toxicomania) is completely different. It takes the form of alterations in behavior, in which the drug and its acquisition become an obsession, everything else taking a secondary position and being worth sacrificing to obtain the drug. Now this type of dependence is extremely rare in individuals who take opioids for chronic pain. Of 11,882 patients who received at least one opioid, there were just four cases of reasonably well-documented psychological dependence, in patients without any history of drug abuse.[10] Studies in patients with non-oncological pain have produced similar results.[11] The origin of psychological dependence also includes other factors besides drugs, such as the type of individual, the reason for using the drug, and the environment, as was clearly documented in American soldiers who, having used heroin during the Vietnam war, abandoned its use when they returned home, without any maintenance programs and with a low rate of recurrence.[6]

In general concepts, whether medical or non-medical, the legitimate and illegitimate use of opioids is not clearly distinguished.[8] Thus, when an opioid is prescribed, if the patient continues to report pain, after what is considered an adequate treatment, then it will probably be considered by the doctor as a case of actual or potential drugaddiction[8]. But pain is a subjective experience, influenced by multiple factors of a physical, psychological, social and spiritual nature. It should not be seen as imaginary or as a maneuver to obtain more analgesics when it appears to be disproportionate to the causal injury, or even where no injury can be detected, or if the pain improves with a placebo or psychological intervention. The patient's report is the most reliable means of assessing the pain, and it cannot be replaced by any objective data, therefore it is necessary to believe the patient and treat the pain that he/she claims to be experiencing. There is not doubt that drug addicted patients with oncological pain pose particular problems, but these are exceptional cases that require specialist intervention.

There is also a fear that opioids will be diverted for illegal use. However, only a very small quantity of illicit products come from the health system, and morphine, particularly its oral forms, is not a drug that is generally used by people with drug addiction.[1]

There also exists a widespread idea that opioids should not be used too early in the disease, because their effect will decrease with repeated use, making them ineffective in the final phase of life when they are more needed; in general, people also see the morphine prescription as a sign that death is close.

In fact, the degree of tolerance is highly variable i.e. the need, with repeated administration, to increase the doses to obtain the same effect, the first sign of which is the reduction of duration of the analgesic effect[6] (tolerance also develops for the side effects, as we shall see below). However, in the stable disease, it is often possible to maintain the same dose, or make small adjustments over weeks or months, and it is observed that in the majority of cases, the need to increase the doses is due to the progression of the disease. Tolerance only becomes problematic if the doctor refuses to prescribe these drugs due to a lack of training in the use, where necessary, of higher than normal doses.[6] There is no justification, therefore, for the attitude that opioids should only be used as a 'last resort', reserved for the terminal phase of the disease.

Opioids can cause multiple side effects, commonly with sedation, nausea, vomiting, constipation, xerostomia, and in rarer cases, respiratory depression, confusion, hallucinations, nightmares, urinary retention, myoclonus, dizziness, dysphoria, itching and inappropriate secretion of anti-diuretic hormone.[9,12] It is likely that the effects that give most concern to patients are those produced on the central nervous system; a fear of loss of mental control. However, sedation, the most common secondary effect, is transitory and often results, in part, in exhaustion of the patient who, with relief from the pain, can finally rest. The potentially most severe secondary effect is respiratory depression. However, it rarely occurs in significant form in patients with intense pain, functioning as a physiological antagonist of respiratory depression[13] and the dose can be increased without fear for as long as the patient is in pain; pain also appears to function as an antagonist of other side effects. Significant respiratory depression is rare, mainly occurring in individuals with acute pain, and those who have never taken opioids, and is accompanied by other signs of CNS depression;[9] with repeated use, tolerance develops quickly in relation to respiratory depression. Constipation is a practically inevitable side effect, for which little or no tolerance develops, therefore it is essential to administer prophylactic laxatives during opioid medication.[6]

Morphine

The objective of treatment of pain is to overcome it. However, it can be useless to establish intermediate levels of control, aiming to achieve, in the initial phase, for example, freedom from pain to enable the patient to sleep the whole night through; then freedom from pain in repose during the day; and finally, freedom from pain on movement (an objective that may be unattainable).

To reach these objectives using the WHO method described above, it is essential to understand that the drugs of the first and second steps of the analgesic ladder have a limit dose, above which no analgesic effect is obtained (with mild opioids some increase in analgesic effect can be obtained, but at the cost of a disproportionate increase in side effects). By contrast, the effect of morphine and other strong opioids is not limited. The effective dose varies greatly, and adequate control of the pain or the appearance of intolerable side effects should be considered as its limit,[14] and not established arbitrarily[13]. Morphine doses can range from 2.5 mg to 2500 mg, or even more, every 4 hours (or the equivalent in controlled release tablets), but the majority of patients require 200 mg or less a day.[15] This range of doses of 1000 times to achieve the objective does not exist in any other area of therapy. [15]

Morphine can be administered by the oral, rectal, subcutaneous (SC), intramuscular (IM), endovenous, intrathecal, epidural, or intraventricular routes, but where possible, the oral route should be preferred. Oral administration is as effective as the parenteral routes when equianalgesic doses are used. When the oral route cannot be used, the most convenient alternative route is SC, if possible via continual drip. The IM route is painful and should only be used in exceptional and isolated cases.

Morphine, when administered orally, is rapidly metabolized in the intestine, and above all, in the liver, the speed varying from person to person, before entering the systemic circulation.

This metabolization does not occur when administered by the parenteral route, therefore smaller doses are needed to obtain the same effect; the ratio of parenteral: oral strength is 2:1 to 3:1 with repeated administration, and the doses should be adjusted when changing from one route to the other.[9] For example, in a patient with intensive pain, where the decision is made to administer morphine by the SC route because the patient presents oral mucositis secondary to chemotherapy, the dose is gradually increased until control is obtained, with 20 mg every

4 hours (in continual drip, administrating the same total dose in 24 hours); after resolution of the mucositis, when changing to the oral route it is necessary to double the dose, which in this case, would be 40 mg every 4 hours of a fast acting morphine, or more conventionally, 120 mg every 12 hours of a controlled release form such as MST (dose of morphine SC every 24 hours = 20 mg x 6 doses = 120 mg; oral equivalent: 120 mg x 2 = 240 mg/24 h =120 mg every 12 hours of MST).

The chronic pain of cancer is generally constant, though it varies in intensity. To over come it, it is essential that the analgesics are taken at the right times, with intervals determined for the duration of their action and latency time, to avoid the reappearance of pain; in an emergency situation, they should only be used as supplementary, and not as exclusive treatment. The analgesic effect of immediate release morphine lasts around 4 hours, therefore it should be administered every 4 hours for the treatment of chronic pain. Controlled release morphine can be used every 12 hours, giving it an obvious advantage for prolonged treatment, but because it reaches its peak of action around 4 hours after ingestion, is not appropriate for acute pain or as a supplement for use in an emergency situation. To determine the therapeutic dose, an immediate release form is preferable, changing to another form afterwards, with the same total dose in 24 hours. However, this is not always possible, particularly in patients who are not admitted, and a controlled release form can be used from the start[11]. The dose can be started with 10, 20 or 30 mg, every 12 hours, depending on the situation, and increased by around a third to half of the previous dose each time, every 24 to 48 hours, until stable analgesia is obtained; ½ tablets of MST should be swallowed whole, and should not be broken or chewed under any circumstances. If the analgesia does not last for 12 hours, the doses should be increased, without reducing the interval between them, although some patients require MST every 8 hours[11,16].

Conclusion

Although effective methods of treating pain exist, which are relatively easy to apply, a high number of cancer patients continue to suffer pain which is inadequately treated. Pain is relegated to a secondary place in the teaching of oncology, which often means it is not properly evaluated, and there is a reluctance to prescribe appropriate analgesics, particularly opioids. There is also a lack of communication, with patients, perpetuating incorrect information and making patients reluctant to take the appropriate analgesics.

It is essential to evaluate pain in cancer patients, and treat it when it occurs, with all the means available, not waiting for the final phase of life, and adapting the therapeutic regime to the patient. Patients should be reassured concerning the possibility that the drug will cause them to lose mental control, or that they will become addicted, and regarding the risk of developing tolerance and as a result not having effective analgesics available later on. ■

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