

# Palliative care; drug treatment in cancer pain

## Abstract

Cancer-related pain is generally described under 3 headings: acute pain, chronic pain and breakthrough pain. Chronic, persistent cancer pain controlled by analgesics throughout the day. When pain is not controlled, it limits the physical activity of the patients, increasing the anxiety and fear of the patients. In this presentation, Drug treatment of cancer pain in palliative care was explained.

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## Introduction

Pain is an unpleasant, emotional, sensory sensation involving all the experiences of a person in the past, accompanied by possible tissue damage from any part of the body.<sup>1</sup> Around 20-35% of the patients diagnosed with cancer, 30-50% of the mid-phase patients, and 60-100% of the late-phase patients are suffering from moderate to severe pain, depending on the type and location of the lesion. The fact that cancer is a deadly disease causes serious fear in patients. In addition, patients are very afraid of dying with pain and suffering. So the pain treatment in cancer patients is an ethical obligation. In recent studies, it has been reported that cancer pain causes restriction of daily activities up to 69% in cancer patients.<sup>2</sup>

## Etiology of pain

Acute pain in cancer patients is usually caused by new metastases and diagnostic and therapeutic interventions, while chronic pain is caused by tumor invasion. No significant pain behaviors and sympathetic activation occur in chronic pain. Affective disorders (anxiety, depression) and vegetative findings (asthenia, anorexia, and sleep disturbances) become prominent during the disease.

## Pain Mechanism

Nociceptive pain is pain associated with tissue damage and nociceptor activation. It may be of somatic or visceral origin. Somatic pain is a sharp and well-localized pain that is caused by skin, subcutaneous, tendon, joint, and muscle.

The visceral pain grows out of organs and cannot be localized well. It is felt in the form of colic, cramp, and compression. Nociceptive pain responds well to nonsteroidal anti-inflammatory drugs and opioids.

Neuropathic pain is pain associated with dysesthesia, autonomic dysfunction, and trophic changes in the manner of as electrical shock and burning in peripheral or central nervous system damage or disease. The pain has a poor response to opioids. Antidepressants and anticonvulsants are the first-line agents in the treatment.

The World Health Organization (WHO) has published a three-step treatment pattern that aims to control the cancer pain and uses adjuvant drugs and non-opioids, weak opioids, and strong opioids as analgesics according to the severity of pain. Analgesics are preferred

according to the type and severity of the pain. The treatment is regulated according to the step system recommended by the World Health Organization.

In this step treatment, it is important to consider that this is a personal treatment when choosing a step according to the severity of the pain. The simplest, safest and cheapest oral route should be preferred primarily for the treatment. It is aimed to ensure that the agents to provide pain control are used all day and to give importance to details. In general, non-opioid drugs such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAID) are used alone or in combination in the first step. The second step is initiated in case the pain cannot be controlled. In addition to the first step, a light, weak-moderate opioid such as codeine is used in the second step. In case the pain persists, it is passed to the third step and a strong opioid and is titrated until the dosage to reduce the pain.<sup>3,4</sup> Rectal, transdermal, subcutaneous, parenteral and intrathecal-epidural routes can be used in patients who cannot take medicine by the oral route, and those with severe nausea-vomiting, and gastrointestinal system pathology.

According to the step principle that the World Health Organization recommends for the cancer pain, parenteral opioids are suggested when the strong opioids administered by the oral route fail, spinal opioids are suggested when parenteral opioids fail, and finally the neurolytic nerve blocks, neuromodulation, and neuroablation methods are used when spinal opioids fail to relieve the pain. Since the invasive procedures have serious complications, it is important that patient selection is appropriate and these procedures are applied by the experienced staff.

## Non-steroid anti-inflammatory drugs (NSAID)

Most of the NSAIDs are weakly acidic and well absorbed by the gastrointestinal mucosa. They cohere to plasma proteins very highly (>95%) and the amount of free drug (active component) is relatively low. The coherence of NSAIDs to plasma proteins may be reduced in various diseases or in patients with hypoalbuminemia. The clearance of NSAIDs is primarily through the hepatic metabolism with the construction of inactive metabolites. Their effects of the first pass from the liver are low and many are discharged from the liver by being

metabolized to their inactive metabolites by oxidation and conjugation. Their side effects have a very wide spectrum and show a very colorful table.<sup>5,6</sup> Most NSAIDs are fully absorbed from the GIS but may slow down with food. Therefore, they are nowadays administered as enteric coated tablets or continuous release preparations. NSAIDs pass into the synovial fluid more slowly and their synovial fluid concentrations are much more stable, and even with short-term medications, they exhibit much fewer fluctuations than the plasma concentration. Some have the property of accumulation in synovium.<sup>5</sup>

### Side effects

**Side effects of the gastrointestinal system (GIS):** Approximately 25% of patients who use these medicines have GIS side effects such as indigestion, burning, dyspepsia, and widespread abdominal pain. In addition, the ulcer formation and the risk of complications (bleeding, perforation, and death) have increased. This risk is reported to be between 3 to 10 times in different studies. Lesions of the gastrointestinal mucosa associated with these drugs are called analgesics or NSAID gastropathy. Local and systemic mechanisms play a common role in the development of these lesions. A direct effect on the gastric and duodenal mucosa may cause epithelial injury and superficial petechiae, and hidden or massive acute bleedings. It also inhibits the COX enzyme and reduces the synthesis of cytoprotective PGs. These PGs increase bicarbonate release and ensure mucosal renewal by increasing superficial epithelial resistance against injury. This results in increased mucosal blood flow and cytoprotective effect. NSAIDs inhibit this mucosal protective mechanisms.<sup>7-9</sup>

**Renal side effects:** NSAIDs inhibit the synthesis of PGE2 and prostacyclin, which have vasodilator effect in the kidney, and cause decreases in the renin secretion and the glomerular filtration rate (GFR). They cause retention by reducing water and salt excretion and may increase the blood pressure of hypertensive patients. These effects can lead to acute renal failure in elders and cause to acute renal failure in high dose NSAID use and reduce the natriuretic, diuretic and antihypertensive effects of these drugs in the thiazide and similar diuretic sites. The risk of renal failure increases if a patient is taking ACE inhibitors and diuretics in particular. NSAIDs may rarely cause more severe renal diseases such as interstitial nephritis, nephrotic syndrome, acute renal failure or acute tubular necrosis.<sup>7,10</sup>

**Hematological system side effects:** NSAIDs can cause antithrombotic effect, slowing of hemostasis, prolonged bleeding time, and, more rarely, aplastic anemia, thrombocytopenia (TSP), agranulocytosis and blood dyscrasias by blocking the thromboxane A2 synthesis. Aplastic anemia has a high rate of mortality, but rarely coexists with NSAIDs except for phenylbutazone or oxyphenbutazone. While TSP coexists with most NSAIDs, all NSAIDs are interfered with the platelet aggregation. While, with aspirin, this effect on the platelet functions is irreversible and seen during the life of thrombocyte, it is more frequent with other NSAIDs when the drug is present in certain amounts. In practice, this means that the platelet functions return to normal after about 3 half-lives of the medicine after NSAIDs have been discontinued and about 4 days after the aspirin has been discontinued.<sup>5,11</sup>

### Opioid analgesics

Opioids are obtained from a plant species of the genus *Papaver somniferum* from the *Papaveraceae* family. These plant species

include natural opioids such as morphine, codeine, thebaine, papaverine, narcotine. Opioids are highly effective analgesics which are easily titrated and provide an acceptable risk/benefit ratio. They are used in the treatment of severe cancer pain regardless of the mechanism of pain. Opioids act by cohering to their specific receptors [ $\mu$  ( $\mu$ ) and  $\delta$  ( $\delta$ ),  $\kappa$  ( $\kappa$ ),  $\sigma$  ( $\sigma$ ),  $\epsilon$  ( $\epsilon$ ) and opioid-like receptors (ORL1)] in the central and peripheral nervous system. In practical use, a classification method is used according to the power of effects supported by the analgesic use guidelines of the WHO. Weakly effective opioids are used in the second step of the WHO. Codeine, dextropropoxyphene, and tramadol are weak opioids. The strongly effective opioids are used in the third step of the WHO. Morphine, fentanyl, hydromorphone, oxycodone, meperidine are from this group. Opioids show significant pharmacological differences. These differences have clinical importance and provide advantages to certain patients in certain conditions.<sup>12</sup>

In general, the thought of opioid addiction, fear of abuse, and fear of side effects limit the opioid use and access particularly of physicians but also health professionals, and patients-patient relatives. From the point of view of the physician, although opioids are probably the most powerful and cheap method of relieving cancer pain, they may not be used at all, may be used far below the therapeutic level, or vice versa because of opiophobia. In addition, the progression of the disease and increased pain due to treatment problems or inadequate dose opioid use due to opiophobia may cause the patient's pain not to cease and increases the drug demand, which may be misinterpreted by the physicians as abduction or addiction.

In patients with mild-moderate severity, codeine, dihydrocodeine, tramadol or propoxyphene are conventionally used as the rapid-release weak opioids. These analgesics include products combined with acetaminophen, aspirin or NSAID. Tramadol is a synthetic analgesic with a centrally effective opioid agonist having the monoaminergic activity. It has a wide spectrum of effects ranging from acute and chronic to moderate to severe pain. In addition to providing effective analgesia, codeine does not cause significant tolerance and addiction, even in chronic use. It is possible to administrate codeine in different doses considering the severity of pain and this is very useful in the step therapy.<sup>13</sup> A limitation in the use of poor opioids is the occurrence of the ceiling effect. The ceiling effect is that despite the increase of the drug dose, the effect of the drug remains constant and only side effects are observed.

Strong opioids have fast and slow release preparations. Morphine, hydromorphone, buprenorphine, methadone, fentanyl, alfentanil, heroin are the strong opioids most widely used in Europe. They can be administered by the oral, parenteral, buccal, transdermal, transmucosal and transnasal routes. Optimal pain control can be achieved by regular administration of the analgesic doses.<sup>14,15</sup>

### Side effects associated with the opioid use

Opioids show many pharmacological differences, but their most important common feature is that they cause similar side effects. The goal of treatment is to establish an accurate balance between the analgesic effect of these agents and their side effects to ensure painlessness with least side effects and increase the quality of life. Side effects vary depending on the opioid used, the route of administration, the dosage, and the personal and genetic variability of the patient.

## There are 4 general approaches to the treatment of side effects

**Dose reduction:** Non opioid/adjuvant analgesics should be added and/or interventional methods should be applied to avoid loss of pain control when the opioid dose is reduced.

**Symptomatic treatment of the side effects:** Symptomatic agents are widely used in the prevention or treatment of the side effects.

**Changing the route of administration:** The route of administration can be changed depending on the side effects. For example, transdermal fentanyl causes less constipation than oral morphine.

**Replacement of the opioid:** The use of an alternative opioid in cases where untreatable side effects occur can reduce side effects and provide effective and safe analgesia.

Nausea-vomiting and constipation are the most common side effects due to opioid use. Nausea and vomiting respond well to antiemetics. Histamine H1 blockers, 5-HT<sub>3</sub> receptor and dopamine antagonists, anticholinergics, corticosteroids are used alone or in combination. Pharmacologic prophylaxis and laxative therapy should be performed with nonpharmacologic methods such as increasing fluid intake for constipation, consumption of fibrous foods. The respiratory depression is the most feared side effect. In patients who are administered opioids for a long time, such side effects do not occur as long as the opioids are titrated in keeping with the pain. The dose that causes respiratory depression is well above the analgesic dose. Sedation or disorders in the cognitive functions are seen at the beginning of the opioid therapy or with the dose increase. Sedation disappears within a few days due to the rapid development of the tolerance. Itching is often seen during the intrathecal use. Antihistamines, 5HT<sub>3</sub> receptor antagonists, naloxone, and nalbuphine can be used. Neurotoxicity is a syndrome with neuropsychiatric symptoms, which is usually seen at high doses and long-term opioid use. In this case, the dose should be reduced. Haloperidol is a good option for the symptomatic treatment. Tolerance has an important place in the physical and psychic addiction. Tolerance is the need for dose increase to achieve the same analgesic response in repeated applications. Tolerance is a normal physiological effect in the chronic opioid use. An alternative opioid should be used when a tolerance problem occurs.<sup>13,16</sup>

Analgesics are used to improve efficacy in cancer pain or to provide supportive care in the step therapy. In the majority of cases, the balance between analgesia and side effects is achieved by changing the strategy. These strategies include the use of analgesic adjuvants too. Analgesic adjuvants should be used and followed up within the experience of the user according to the type and location of the pain, taking into account the general and psychological state of the patient, rather than being prescribed at a certain dose in each case. Initiating the treatment with a single medication is accepted for a better analgesic response and less risk of toxicity.

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## Conflict of interest

The author declares there is no conflict of interest.

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