



Pharmacotherapy of Cancer Pain With Opioid Analgesics

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SUMMARY

Introduction: Selection of analgesics should be based on the World Health Organization (WHO) analgesic ladder, beginning with non-opioid analgesics in combination with adjuvants for mild pain, weak opioids with adjuvants are indicated for moderate pain, while potent opioids, non-opioids and adjuvants are recommended for severe pain.

Methods: The facts presented in this paper are expanded by searching for recent literature data in the following index-data-bases: SCI index, PubMed, Google Scholar, Scopus, and by using adequate key words. The idea supporting this paper was to make practice easier for clinicians who are engaged in supportive oncology and to help in adequate and up-to-date malignant pain management in oncology patients in everyday practice.

Topic: Initial opioid dose should be low, and long-acting opioid dose should be gradually increased and titrated considering daily requirements of short-acting opioid formulation due to pain breakthrough. It is mandatory for patients on long-acting opioid treatment to be provided with fast-acting medication for breakthrough pain treatment. The following long-acting strong opioids formulations are available in Serbia - oxycodone, oxycodone/naloxone fixed combination, hydromorphone, tapentadol, fentanyl. A patient and his/her family should be warned about possible side effects of opioids, primarily morphine. There is great fear of prescribing opioid analgesics due to their possible side-effect of respira-

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tory depression. Opiophobia is defined as exaggerated concern about the consequences of medical use of opioids. The risk of opioids is estimated to outweigh the benefits of the treatment, resulting in the fact that they are not used where indicated. Avoiding opioid prescriptions is one of the biggest barriers for successful treatment of cancer pain.

Conclusion: Oncology patients with moderate and severe pain have a constitutional right not to tolerate pain and they have a right to strong opioid treatment. Implementation of analgesic elevator is recommended. There should not be any fear of addiction or other side-effects that can be controlled, and the benefits greatly outweigh the risks of possible side-effects in these patients. Cancer pain management should be an equally important element of overall cancer treatment. Only by multimodal and multidisciplinary treatment approach satisfactory analgesic effects may be achieved while minimizing adverse side-effects.

Keywords: Opioids, Analgesic Ladder, Analgesic Elevator, Side Effects, Interactions, Opiophobia

INTRODUCTION

Current pharmacotherapy of chronic cancer pain means that each oncology patient is a unique individual, so personalized medicine and individualized treatment should be taken into account when choosing adequate pharmacotherapy, according to following guidelines: drug efficacy, drug safety, routes of administration, potential drug interactions with existing therapy, possible side-effects, risk of overdose and abuse, patient adherence and price [1].

Selection of analgesics should be based on the World Health Organization (WHO) analgesic ladder, beginning with non-opioid analgesics in combination with adjuvants for mild pain, weak opioids with adjuvants are indicated for moderate pain, while potent opioids, non-opioids and adjuvants are recommended for severe pain [2].

The five basic recommendations for the management of this kind of pain recommended by the WHO include: oral administration of analgesics whenever possible, taking analgesics at regular intervals, analgesics should be selected according to analgesic ladder, individual approach to the patient, and detailed keeping of medical documentation [3].

Serbian National Guidelines for the diagnosis and treatment of chronic cancer pain also indicate administration of opioids in patients with pain intensity >4/10 according to Numeric Pain Rating Scale (NPRS). In chronic cancer pain it is recommended to administer long-acting opioid formulations, while short-acting opioid formulations are used only initially to titrate analgesic dose and for breakthrough pain treatment [4].

It is necessary and safe to combine opioid analgesics with non-opioids and adjuvant analgesics, such as: paracetamol (max 4 grams daily, but special attention should be paid to paracetamol dosing since it can be hepatotoxic in overdoses), non-steroidal anti-inflammatory drugs (especially when available in liposomal formulation due to their improved and long-acting effects and fewer side-effects), long-acting corticosteroids with implementation of dose de-escalation at treatment discontinuation due to potential side-effects; antiepileptic agents, primarily gabapentinoids (gabapentin and pregabalin as most commonly prescribed co-analgesic with shorter dose-titration period time than gabapentin), antidepressants for the treatment of neuropathic component of pain (duloxetine and venlafaxine, while amitriptyline from tricyclic antidepressants group is avoided due to its poor safety regarding cardiotoxicity), bisphosphonates (zoledronic acid), capsaicin locally. Also, in these patients it is necessary to provide supplementation with, for example, B-complex vitamins, alpha-lipoic acid, palmitoylethanolamide (PEA) etc. [5-9]. Apart from these, the use of cannabinoids has been approved in some countries as adjuvants in supportive treatment of oncology patients. It is necessary to license the use of synthetic cannabinoids in our country as well, and to educate healthcare professionals, starting with medical students who lack formal education related to this medical field [10]. Drugs from this group are so called new psychoactive substances that are greatly abused, resulting in frequent acute intoxications and addiction. It is necessary to raise awareness of healthcare and legal frame-

work to new psychoactive substances, strongly address indications for their use, professional education and to diminish phobia regarding this group of drugs, strictly ensuring all pharmacovigilance methods during administration of these drugs [11].

Additional combination of opioids and benzodiazepines should be carefully considered due to drug-to-drug interaction, since it has been proved that alprazolam, as one of prescribed drugs from this group, greatly increases monthly total number of traffic accidents, but only if given as monotherapy anxiolytic [12].

The aim of pharmacological treatment of cancer pain can be reflected in: reducing pain intensity, relieving insomnia (improving sleep), eliminating associated depression and anxiety, and improving quality of life of these patients [13].

METHODOLOGY

This paper was designed as a short educational review of this common pharmacotherapeutic problem in everyday oncology practice, with special emphasis to opioid analgesics. The facts presented in this paper are expanded by searching for recent literature data in the following index-data-bases: SCI index, PubMed, Google Scholar, Scopus, and by using key words – cancer pain, pharmacotherapy, analgesia, opioid analgesics. The idea supporting this paper was to make practice easier to clinicians who are engaged in supportive oncology and to help in adequate and up-to-date malignant pain arresting in oncology patients in everyday practice, and to minimize the prevalence of opiophobia.

TOPIC

Analgesic elevator

Apart from the aforementioned WHO analgesic system, in everyday clinical practice nowadays the system of analgesic elevator is often used, enabling the switch from the first to third ladder, or immediate treatment transition from non-opioid analgesics to strong opioids, which has proved to be justified and safe in everyday clinical practice.

Initial opioid dose should be low and long-acting opioid dose should be gradually increased and titrated considering daily re-

quirements of short-acting opioid formulation due to pain breakthrough (1/6 of long-acting opioid total daily dose). It is mandatory for patients on long-acting opioid treatment to be provided with fast-acting medication for breakthrough pain treatment [14].

For this therapeutic indication extended-release opioids are recommended because they have: prolonged time before reaching maximum drug plasma concentration, decreased fluctuations of drug concentration, prolonged analgesia within therapeutic response, decreased risk of potential toxicity and respiratory depression, decreased potential abuse, dosing is less frequent and it makes patient adherence to the treatment better, as well as stable plasma drug concentration in correlation of analgesia duration.

Opioid analgesics

The following long-acting strong opioids formulations are available in Serbia – oxycodone, oxycodone/naloxone fixed combination, hydromorphone, tapentadol, fentanyl.

Hydromorphone is a semisynthetic derivative of morphine exhibiting its main pharmacological effects on the CNS and smooth muscles. It is mostly an agonist of μ -receptor, with much weaker affinity for κ -receptors. Oral hydromorphone is about 5 times more potent than morphine. After oral administration of hydromorphone extended-release tablets, plasma concentrations gradually increase over 6 – 8 hours, and concentrations are sustained for about 18 – 24 hours after the intake of the drug dose. Drug is then absorbed from the intestinal tract over 24 hours approximately, which is consistent with once-daily oral dosing. The mean absolute bioavailability of hydromorphone after a single dose of 8 mg, 16 mg, or 32 mg of hydromorphone is in the range from 22% to 26%. Steady-state plasma concentrations are approximately twice as high as those achieved after the first dose, and steady-state is reached after the fourth dose of hydromorphone. Time-dependent changes in pharmacokinetics were not registered with multiple dosing. The level of binding for plasma proteins is low. Glucuronidation is the main metabolic pathway, and the principal metabolite is hydromorphone 3-glucoronide which remains in plasma similar to hydromorphone. Unlike morphine, no 6-glucuronid is produced by hydromorphone metabolism.

Hydromorphone is available in Serbia as a long-acting formulation taken every 24 hours [15].

Long-acting fixed combination of strong opioid analgesic oxycodone and opioid antagonist naloxone at a dose twice lower than opioid dose, binding to opioid receptors in gastrointestinal tract and not affecting naloxone analgesic effect is available in Serbia for severe cancer pain. Long-acting formulation of pure oxycodone with no higher bioavailability than oxycodone from fixed combination, as well as short-acting oxycodone capsules for breakthrough pain treatment are also available [16].

Oxycodone is a semisynthetic opioid analgesic that undergoes active transport across the blood-brain barrier and reaches high concentrations in the brain. It has twice the analgesic effect than morphine, and its bioavailability is 75%. It is available in long-acting and short-acting formulations. It also has better tolerability and fewer side effects than morphine. Oxycodone is primarily metabolized by isoenzyme CYP3A4 and partially by CYP2D6. The activities of these metabolic pathways may be inhibited or induced by concurrent use of various drugs and food. Biotransformation in the liver by isoenzyme CYP2D6 produces metabolites – oxymorphone (active) and noroxycodone (inactive). CYP3A4 inhibitors, such as macrolide antibiotics (clarithromycin, erythromycin, telithromycin), azole antimycotics (ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir), cimetidine, and grapefruit juice may cause reduction of oxycodone clearance and increase oxycodone plasma concentrations. CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, and St John's Wort) may induce oxycodone metabolism and provoke increased drug clearance, resulting in reduced oxycodone plasma concentration. So, caution is warranted, and additional titration may be needed to achieve optimal control of symptoms. Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine, and quinidine may cause oxycodone clearance reduction and result in increase of oxycodone plasma concentration [17].

Tapentadol (3-dimethylamino-1-ethyl-2-metil-propil-fenolhydrochloride) is a novel opioid analgesic at Serbian market. Its analgesic effect is reached by a dual mechanism – typical mu-opioid receptor agonism

and inhibition of noradrenaline reuptake. Such a mechanism of action relieves both nociceptive and neuropathic components of so called mixed cancer pain. Thus, its analgesic effect is reached by reducing ascending pain signals and increasing descending pain inhibition. In this way adequate analgesia is reached, with few side effects [18].

After tapentadol oral administration, about 70% of the dose is excreted in urine as conjugated forms (55% glucuronide and 15% sulfate of tapentadol). Uridine diphosphate glucuronyl transferase (UGT) is the main enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, further metabolized by conjugation. None of the metabolites contributes to the analgesic activity. In vitro testing did not show any potential of tapentadol, either to induce or inhibit cytochrome P450 enzyme. So, it is unlikely that clinically relevant interactions mediated by the cytochrome P450 system may occur. According to this, minimal drug-to-drug interaction potential of this drug with all the drugs metabolized by cytochrome P450 system is based [19].

It is not recommended to use long-acting tapentadol formulation along with short-acting formulation of the same drug, but traditional opioids for breakthrough pain instead. This drug is indicated to mixed cancer pain. The immediate-release formulation of tapentadol is not used at all in the treatment of chronic cancer pain [20].

Transdermal opioid formulations are definitely not the first therapeutic option and are not recommended as first-line therapy for treating cancer pain in patients without swallowing difficulties. Transdermal fentanyl (this pharmaceutical formulation is possible due to its lipophilicity) is the only safe long-acting opioid analgesic available in Serbia in 4 dosage forms in patients with end-stage renal failure. It is recommended to apply the patches at different areas of the skin than previously used. They are last-line therapy for patients who were not on opioid treatment as well. Transdermal buprenorphine formulation is available in some countries worldwide. These formulations are mostly intended for patients with aphagia in terminal cancer phase and to whom transdermal opioid prescriptions are

indicated, since oral opioid formulations must be swallowed whole, and not crushed or broken [21].

The fentanyl patch provides continuous systemic release of fentanyl during a 72-hour period following application. The skin under the patch absorbs fentanyl, and fentanyl depot is formed in the upper skin layers. After that fentanyl becomes available to the systemic circulation. The polymer matrix and fentanyl diffusion through the skin layers guarantee that the release rate is relatively constant. The average bioavailability of fentanyl after transdermal patch application is 92%. After the first patch application, serum fentanyl concentrations increase gradually, they are generally balanced between 12 and 24 hours and remain relatively constant for the remaining 72-hour-application period. By the end of second 72-hour application, serum concentration balanced-state is reached and maintained during the following applications of patches of the same size. A rise in skin temperature may increase the absorption of transdermally applied fentanyl. Fentanyl is quickly distributed in various tissues and organs. Fentanyl accumulates in skeletal muscles and fat and then it is slowly released into blood. Plasma protein binding was 95% on average. Fentanyl easily crosses blood-brain barrier. It also goes through the placenta and is excreted in breast milk [22].

Fentanyl is an active substance with a high clearance activity that is quickly and largely metabolized primarily by CYP3A4 enzyme in the liver. The primary metabolite, norfentanyl, and other metabolites are inactive. Skin does not metabolize transdermal fentanyl. After a 72-hour patch application, the mean fentanyl half-life elimination is in the range from 20 to 27 hours. In the period of 72 hours since intravenous fentanyl application, about 75% of the dose is excreted into the urine and about 9% into the faeces. Excretion is primarily in the form of inactive metabolites.

Concomitant use of fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitor may result in increased fentanyl plasma concentrations. Generally, patients should wait 2 days after discontinuation of CYP3A4 inhibitor therapy before applying the first patch. However, inhibition duration varies and in some CYP3A4 inhibitors with a long elimination half-life, such as amiodarone, or for time-dependent inhibitors such as erythromycin, idelalisib, nicardipine and ritonavir, duration

of this period may need to be longer. Patient treated with fentanyl patch should wait at least 1 week after last patch removal before the initiation of CYP3A4 inhibitor treatment [23].

As for rapid-onset opioid formulations in Serbia, morphine-sulfate for oral application and oxycodone are available. A rapid-onset oxycodone formulation is recommended for this indication if the patient is intolerant to morphine, the same applies to breakthrough pain treatment. Then, according to patients' daily needs for short-acting morphine, they should be switched to some strong long-acting opioid analgesic by equi-analgesic doses of morphine using available equi-analgesic tables [24]. Long-acting analgesics are recommended as therapy initiation in these patients, in whom the pain had previously been kept under control with at least 60mg of oral morphine/24h.

Morphine is a drug belonging to the group of strong opioid analgesics. Weak opioids are called weak because they have upper limit beyond which efficacy is not increased, that is, there is a maximum daily dose that can be applied and they are used to treat pain of 5 to 6 intensity according to NRS. Strong opioids do not have maximum daily dose and are used for moderate to severe pain. Morphine is a pure opioid agonist, *Papaver somniferum* natural derivative specific for μ opioid receptors (OP_3). OP_3 receptors are evenly distributed throughout all the neuraxis and have an important role in analgesia, CV and respiratory functions, peristalsis, mood, thermoregulation, and hormone secretion. Interaction between morphine and these receptors in the central nervous system eliminates pain and relieves reaction to pain in patients.

Morphine demonstrate analgesic effect and it is indicated in most severe pain as a specific sensory experience. It produces dose-dependent effects on psychomotor performance and, depending on the dose, causes sedation (>10 mg), or sometimes agitation (<10 mg). Besides analgesia, at higher doses it may cause sleepiness, but it does not cause generalized CNS depression nor loss of consciousness. Morphine causes toxicomania, drug tolerance, physical and psychological dependence. Starting with therapeutic doses, morphine produces respiratory center depression by decreasing its sensitivity to CO_2 . It stimulates the vomiting center and suppresses cough center. Morphine causes myosis of central origin, what is

also a sign of chronic intoxication.

Morphine decreases tonicity and peristalsis movement of longitudinal fibers and increases tonicity of circular fibers, causing constipation. It causes spasm on sphincters (pylorus, ileocecal valve, anal sphincter, Oddi sphincter, vesical sphincter), that is constipation, increased pressure in the biliary tract, urinary tract spasm.

Oral morphine sulfate is quickly absorbed from the digestive tract. Distribution in the body is extensive, especially to kidneys, liver, lungs, and spleen, while its concentrations are lower in muscles and brain because only small quantities cross the blood-brain barrier (hematoencephalic barrier). First-pass metabolism through the liver is important, so systemic availability is about 25%. The main pathway of morphine metabolism is conjugation with glucuronide derivatives at the 3- and 6- position. About 10 % of morphine dose is excreted in the faeces. The remaining part is excreted in urine, mostly in conjugated form. About 90 % of a single dose of morphine is excreted after 24 hours [25].

If parenteral morphine is administered, 1/3 of the peroral dose is given since liver metabolism is avoided, so bioavailability is increased. Starting oral morphine dose for the first administration is 5mg/6h, with previous opioid use 10 mg/6h, when satisfactory analgesia is achieved switch to long-acting opioid and convert it to morphine equivalent dose for 24h [26].

Among weak analgesics in the Republic of Serbia, tramadol is available for independent use or as fixed dose non-opioid combination tramadol/paracetamol – indicated for moderate pain treatment. Treatment of moderate cancer pain starts with tramadol as a weak opioid analgesics relative to pain intensity. If the pain is not adequately controlled even with the maximum dose of 400mg tramadol, or if there are intolerable adverse effects, it is recommended to switch the patient to morphine. Alternatively, pharmacotherapy of moderate pain may be initiated with low morphine doses (analgesic elevator has been proved safe in everyday clinical practice). In the titration phase short-acting oral morphine formulations are recommended, when more rapid pain relief is needed, and as interventional pain management for breakthrough pain [27].

Tramadol is an opioid analgesic that acts in the central nervous system. It is a non-

selective pure agonist at μ , δ and κ opioid receptors, with a higher affinity at μ receptors. Other mechanisms involved in its analgesic effects are inhibition of noradrenaline re-uptake and increased serotonin release. Tramadol has antitussive effect. Unlike morphine it does not cause respiratory depression at wide range of analgesic doses. Similarly, gastrointestinal motility is not drastically altered. The potency of tramadol is believed to be one tenth to one sixth that of morphine.

The racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability after the first single oral dose is about 75%. After repeated doses bioavailability increases to about 90%. After oral administration of tramadol/paracetamol combination, paracetamol absorption is rapid and nearly complete, taking place mainly in the small intestine. Maximum paracetamol concentrations are reached in 1 hour and are not changed by concomitant use with tramadol. Concomitant oral administration of tramadol/paracetamol combination with food does not have significant effect on maximum concentration nor does it prolong absorption of tramadol or paracetamol. Thus, this combination may be used independently of the meal times.

Tramadol is greatly metabolized after oral administration. About 30% of the dose is excreted in urine as unchanged drug, while 60% of the dose is excreted as metabolites. Tramadol is metabolized through O-demethylation (catalyzed by the enzyme CYP2D6) of the metabolite M1, and N-demethylation (catalyzed by CYP3A4) of the metabolite M2. The metabolite M1 has analgesic features and is more potent than original drug. The plasma concentrations of M1 are several times lower than those of tramadol, so its contribution to clinical effects is unlikely, even with multiple doses [28].

Side-effects, overdose, interactions

A patient and his/her family should be warned about possible side effects of opioids, primarily morphine.

There is great fear of prescribing opioid analgesics due to their possible side-effect of respiratory depression (reduced sensitivity of the respiratory center to carbon-dioxide), however, it has been shown in clinical practice that tolerance this effect occurs rapidly.

Table 1. Available opioid analgesics in the Republic of Serbia intended for the pharmacotherapy of cancer pain

Opioid analgesic/fixed combination of opioid with non-opioid or opioid antagonist	Available pharmaceutical formulation	Dosage formulation	Opioid type	Maximum daily dose
Tramadol	capsules	50mg	weak short-acting	400mg
Tramadol	tablets	100mg 150mg	weak long-acting	400mg
Tramadol	ampulla	50mg/ml 100mg/ml	weak short-acting	400mg
Tramadol/paracetamol	tablets	37.5mg/325mg	weak opioid + non-opioid analgesic	150mg/1300mg
Tramadol/paracetamol	tablets	75mg/650mg	weak opioid + non-opioid analgesic	300mg/2600mg
Oxycodone	tablets	5mg 10mg 20mg	Strong long-acting	180mg
Oxycodone	capsules	5mg 10mg 20mg	Strong short-acting	80mg
Oxycodone/naloxone	tablets	5mg/2,5mg 10mg/5mg 20mg/10mg 40mg/20mg	Strong long-acting	160mg/80mg
Tapentadol	tablets	50mg 100mg 150mg	Strong long-acting	500mg
Tapentadol	tablets	50mg 75mg 100mg	Strong short-acting	700mg
Fentanyl	Transdermal patch	25mcg/h 50mcg/h 75mcg/h 100mcg/h	Strong long-acting	none
Morphine sulfate	Oral formulations - drops and syrup	Oral drops - 20mg/ml Syrup - 10mg/5ml	Strong short-acting	none

It is well known that administration of morphine may lead to the development of tolerance and addiction. Withdrawal syndrome may occur after sudden cessation of therapy, or at administration of opioid antagonist, such as naloxone. Morphine sulfate is an opioid agonist and a controlled drug. Such drugs are subject to abuse by patients with history of abuse. Use of opioid analgesics may be accompanied by physical and/or psychological dependence and tolerance development. Symptoms may be relieved by dose reduction, or change in dosage form, as well as by gradual morphine withdrawal.

The characteristics of opioid withdrawal are: restlessness, yawning, sweating, chills, myalgia, mydriasis and palpitations, irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhea, increased blood pressure, increased respira-

tory rate or heart rate [29].

Morphine overdose treatment is intravenous naloxone administration. This treatment may be repeated at 2-3 minute interval if necessary, or changed by an infusion of naloxone in 100 mL of saline solution or 5 % glucose solution. Always ensure that airways are maintained. Peak plasma concentrations are expected within 15 minutes of oral intake. Thus, it is unlikely that gastric lavage and activated charcoal will be beneficial. The duration of naloxone effect (2-3 hours) may be shorter than the duration of the morphine overdose effects. It is recommended to observe the patient who regained consciousness after naloxone administration for at least 6 hours after the last dose of naloxone [30].

Concomitant use of opioid analgesics with MAO inhibitors due to central excitation symptoms resembling serotonergic syndrome causes: diarrhea, tachycardia, sweating, trem-

bling, confusion, and coma. In case of recent treatment with MAO inhibitors, tramadol treatment should only start two weeks after MAO inhibitors discontinuation. Their concomitant use is also not recommended with: alcohol, since it increases the sedative effects of opioid analgesics; carbamazepine and other enzyme inducers because of reduced efficacy risk and shorter duration of efficacy due to decreased plasma concentrations of tramadol; opioid agonists-antagonists (nalbuphine, pentazocine) due to decreased analgesic effect by competitive blocking effect at the receptors, with the risk of withdrawal syndrome occurrence; other central nervous system depressants, such as other opioid drugs (including cough suppressants and substitutive therapies), barbiturates benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, and sedative antihistamines, neuroleptics, centrally-acting antihypertensives, thalidomide and baclofen, since these drugs may cause increased central depression. Caution is warranted with opioid administration in patients with head injuries, prone to convulsions, in a state of shock, in an altered state of consciousness of unknown origin, with respiratory center or respiratory function disorder, with an increased intracranial pressure [31].

According to all aforementioned, characteristics of an ideal opioid would be: short half-life, long-acting effects, predictable pharmacokinetics, no clinically significant metabolites, rapid-onset, easy titration, without „plateau” drug dose, with minimum side effects.

The only side-effect of opioids that does not develop tolerance is chronic opioid-induced constipation that poses a huge problem in clinical oncology practice. This symptom usually occurs within complex opioid induced bowel dysfunction (OIBD) affecting about 90% of patients chronically treated with opioids. In these patients, due to opioid receptors agonism, in gastrointestinal tract by opioid agonists, longitudinal propulsive peristalsis is affected, sphincter tonus is increased, luminal content changed, leading to increased absorption and decreased gut secretion.

Prophylactic laxatives that should be prescribed concurrently with opioid analgesics, do not eliminate the cause of opioid-induced bowel function disorder. They are mostly ineffective and may result in additional side-effects, and their only target is colon.

Over 50% of patients are not satisfied with laxative administration [32].

Macrogol is recommended for treating this type of constipation.

Opiophobia

Opiophobia is defined as exaggerated concern about the consequences of medical use of opioids. The risk of opioids is estimated to outweigh the benefits of the treatment, resulting in the fact that they are not used where indicated (pain management and palliative care).

Avoiding opioid prescriptions is one of the biggest barriers for successful treatment of cancer pain. In practice, opiophobia mostly refers to morphine phobia.

Opiophobia in patients – patients are concerned about development of addiction, opioid side-effects and development of tolerance. They fear that opioid administration is suggestive of terminal phase of the disease. The prejudice that we should tolerate pain and that acceptance of strong opioid treatment means that the patient is „weak” is widespread.

At the moment of initiating a strong opioid therapy patients should be asked about their concerns and they should be offered information on opioid analgesics efficacy and their safety as well in the management of cancer pain. Patients should be given information on cancer pain and opioid pain treatment, and encouraged to be actively involved partners in pain treatment.

Opiophobia among healthcare professionals is quantified by the numeric rating scale 1-10, where 1-4 indicates mild concern, 5-10 moderately strong and strong concern. This scale was used to express the level of concern for tolerance development, respiratory depression, other side-effects of opioids, as well as restrictions in opioid legislation.

In comparison to doctors, a significantly greater number of nurses show moderately strong and strong concern for tolerance development, respiratory depression, other side-effects of opioids, as well as restrictions in opioid legislation [33].

Moderately strong and strong concern regarding restrictions in current regulations for opioid prescriptions prevails among doctors.

CONCLUSION

Oncology patients with moderately strong and strong pain have a constitutional right not to tolerate pain and they have a right to strong opioid treatment. Painkiller therapy should not be delayed, implementation of analgesic elevator is recommended. There should not be any fear of addiction or other side-effects that can be controlled, and the benefits greatly outweigh the risks of possible side-effects in these patients. Each patient is a unique individual and individually tailored optimal dose for every single patient should be achieved.

Pain greatly affects patients' quality of life by its physical and emotional component as well. Cancer pain management should be an equally important element of overall cancer treatment. Only by multimodal and multidisciplinary treatment approach satisfactory analgesic effects may be achieved while minimizing adverse side-effects.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Farmakoterapija kancerskog bola opioidnim analgeticima

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KRATAK SADRŽAJ

Uvod: Izbor analgetika treba da se zasniva na analgetskoj lestvici Svetske zdravstvene organizacije (SZO), počevši od neopioidnih analgetika u kombinaciji sa adjuvansima za blagi bol, slabi opioidi sa adjuvansima su indikovani za umereni bol, dok su snažni opioidi, neopioidi i pomoćna sredstva preporučeni za teške bolove.

Metodologija: Činjenice predstavljene u ovom radu su proširene pretragom novijih literaturnih podataka u sledećim indeksnim bazama podataka: SCIndex, PubMed, Google Scholar, Scopus i korišćenjem adekvatnih ključnih reči. Ideja koja je podržavala ovaj rad je bila da se olakša praksa kliničarima koji se bave suportivnom onkologijom i da se u svakodnevnoj praksi pomogne u adekvatnom i ažurnom otklanjanju malignih bolova kod onkoloških pacijenata.

Tema: Početna doza opioida treba da bude niska, a dozu dugodelujućeg opioida treba postepeno povećavati i titrirati uzimajući u obzir dnevne potrebe za formulacijom kratkododelujućih opioida zbog proboja bola. Obavezno je da pacijenti koji su na terapiji dugodelujućim opioidima treba dobiju lekove sa brzim dejstvom za lečenje proboja bola. U Srbiji su dostupne sledeće formulacije jakih opioida dugog dejstva - oksikodon, fiksna kombinacija oksikodon/nalokson, hidromorfon, tapentadol, fentanil. Pacijenta i njegovu porodicu treba upozoriti na moguće neželjene efekte opioida, prvenstveno morfina. Postoji veliki strah od propisivanja opioidnih analgetika zbog njihovog mogućeg neželjenog efekta respiratorne depresije. Opiofobija se definiše kao preterana zabrinutost za posledice medicinske upotrebe opioida. Procenjuje se da rizik od opioida prevazilazi koristi od lečenja, što rezultira činjenicom da se ne koriste tamo gde je indikovano. Izbegavanje propisivanja opioida je jedna od najvećih prepreka za uspešno lečenje kancerskog bola.

Zaključak: Onkološki pacijenti sa umereno jakim i jakim bolom imaju ustavno pravo da ne trpe bol i na terapiju jakim opioidima. Preporučena je primena analgetičkog lifta. Ne bi trebalo da postoji strah od zavisnosti ili drugih neželjenih efekata koji se mogu kontrolisati, a koristi uveliko nadmašuju rizike mogućih neželjenih efekata kod ovih pacijenata. Lečenje kancerskog bola trebalo bi da bude podjednako važan element ukupnog lečenja onkoloških pacijenata. Samo multimodalnim i multidisciplinarnim pristupom lečenja mogu se postići zadovoljavajući analgetski efekti uz min-

imiziranje neželjenih nuspojava.

Ključne reči: opioidi, analgetska lestvica, analgetski lift, neželjeni efekti, interakcije, opiofobija

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