Pharmacologic management of pain

MARIJAN PUŠELJIĆ
UNIVERSITY OF ZAGREB SCHOOL OF MEDICINE

DOI: http://dx.doi.org/10.17486/gyr.3.1021

SUMMARY: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. While acute pain has a physiological role in alerting people about ongoing pathological processes, chronic pain has lost this role and serves no physiological function. Chronic pain associated with some comorbidities and affect a person's quality of life. According to the available algorithms for the treatment of pain, drug therapy should start with the application of non-steroidal anti-inflammatory drugs. If the pain persists or worsens it is necessary to start the usage of opioid analgesics. Therapy should start with the lowest possible dose and used in the shortest possible period in order to avoid any unnecessary side effects. Successful treatment of pain requires a good knowledge of the pharmacokinetics and pharmacodynamics of every drug used in the therapy.

KEYWORDS: Chronic pain, NSAID, Opioids, Pharmacotherapy

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. [1] It's a subjective feeling and even considered as a fifth vital sign. [2] For many patients the word ˝pain˝ has the meaning of disease and suffering.[1] Each person's reaction to pain is individual and the severity of pain does not correlate with the actual degree of tissue damage.[3] The emotional state, circumstances under which the pain was acquired, and whether it is perceived as a threatening signal, can modulate the perception of pain. Acute pain doesn't represent a public health problem and it isn't related to a reduced life quality, while chronic pain can significantly affect a person's quality of life. It's related to many physiological and social alterations, including sleep disturbance, loss of appetite, decreased libido, fatigue, mental exhaustion, depression, anxiety, irritability and reduced social life.[1] According to the World Health Organization (WHO) study in primary care settings across the world, approximately one-fifth of all primary care patients suffer from persistent debilitating pain, and they are four times more likely to have comorbidities like anxiety or depression than pain-free primary care patients.[4] The treatment of acute and chronic pain has an important place in clinical medicine. This review is focused on the pharmacological methods of pain treatment because this approach is the first and most common method used by physicians in their everyday practice.

Pain mechanism and classification

There are two main types of pain, nociceptive and neuropathic pain. Nociceptive pain is caused by direct stimulation of peripheral nerve ending by noxious stimulus such as trauma, burns or ischaemia.[3] Nociceptors are simple structures found at the end of nerve fibers in the skin, periosteum, joint capsule, meninges, pleura, peritoneum, organ walls and other structures. After stimulation impulses are transmitted to the dorsal horn of the spine, where they synapse with the dorsal horn neurons in the substantia gelatinosa and ascend to the brain. The basic pain sensation occurs in the thalamus, which is connected to the cortex and to the limbic system.[1] Neuropathic pain is caused by a dysfunction of the pain perception system within the peripheral or central nervous system as a result of injury, disease or surgical damage.[3] It's commonly associated with diabetes, chemotherapy, herpes zoster infection, chronic alcohol abuse and other idiopathic conditions, such as idiopathic small fiber neuropathy and trigeminal pain.[5] Pain can also by divided into acute, which lasts less than 3 months, and chronic, which lasts more than 3 months.[1] Chronic pain persists beyond the expected normal time for healing and serves no useful physiological purpose.[6]

Pharmacotherapy of pain

Many of the principles or algorithms for pain management can be applied to any type of pain, but there are distinct differences between the management of acute, chronic and palliative pain. Acute pain should be treated with medication that causes no unnecessary side effects or any additional risks for the patient. Chronic non – malignant pain is more difficult and even impossible to relieve all pain without causing any side effects. Pain management should be more orientated towards non pharmacological methods.[3] Opioids are commonly used for chronic malignant pain and for palliative care. Multi-target pharmacology is probably the best way to treat pain, because it affects more than a single pathogenetic mechanism and allows keeping a much lower dose of a single drug that could otherwise cause some side effects in higher doses. Drugs with a dual mechanism of action, such as tapentadol, should be prefered for management of chronic pain.[6] WHO published in 1986 and 1996 a conceptual model to guide the management of cancer pain called the WHO pain ladder. It's also used as a guideline for the treatment of non – cancer pain. The ladder proposes the use of non-opioid medications as a first line treatment. A weak opioid drug must be administrated if the pain persists or worsens. The next step is the use of a more powerful opioid drug. Taking two drugs of the same pharmacological

Non – selective COX inhibitors	Dose
Aspirin	40-80 mg/d (antiplatelet) 1g/ 4-6h (anti-inflammatory)
Paracetamol	500 mg/ 4 x d
Indomethacin	50-70 mg/ 3 x d
Ibuprofen	600 mg/ 4 x d
Ketoprofen	70 mg/ 3 x d
Naproxen	375 mg/ 2 x d
Sulindac	200 mg/ 2 x d
Diclofenac	50-75 mg/ 4 x d
Piroxicam	20 mg/ d
Meloxicam	7.5-15 mg/ d
Selective COX – 2 inhibitors	**Dose**
Celecoxib	100-200 mg/ 2 x d

Table 1 – NSAIDs and the recommended dose. [8,15]

Strong Agonists		Duration of analgesia (hours)
Phenanthrenes	Morphine	4-5
	Hydromorphone	4-5
	Oxymorphone	3-4
Phenylheptylamines	Methadone	4-6
Phenylpiperidines	Fentanyl	1-1.5
	Sufentanyl	1-1.5
	Alfentanyl	0.25-0.75
	Remifentanyl	0.05 (3-4 min)
	Meperidine	2-4
Morphinas	Levorphanol	4-5
Mild to moderate agonists		**Duration of analgesia (hours)**
Phenanthrenes	Codeine	3-4
	Dihydrocodeine	3-4
	Hydrocodone	4-6
	Oxycodone	3-4
Phenylheptylamines	Propoxyphene	6
Phenylpiperidines	Diphenoxylate	12-14
	Loperamide	7-14

Table 2 – Opioid analgesics and the duration of analgesia. [8, 15]

category should be avoided. The analgesic ladder also includes the possibility of adding adjuvant treatments for neuropathic pain or for symptoms associated with cancer (steroids, anxiolytics, antidepressants, hypnotics, anticonvulsants, antiepileptics and other types).[7] It is vital that the patients concerns about opioids are explored. Patients should be reassured that, when they are used for pain, psychological dependence and tolerance can develop, but are extremely rare in patients with no previous history of addiction.[3]

The cornerstone of the WHO document rests on 5 simple recommendations for the correct use of analgesics to make the prescribed treatments effective. Analgesics should be administered per os and given at regular intervals. The prescription must be given according to the level of the patient's pain and not according to the medical staff's perception of the pain. The dosing must be individual and the patient, including his family, must receive detailed instruction about the drug and schedule of administration.[7]

Non – opioid analgesics

Non – opioid medications include paracetamol (acetaminophen) and non steroid anti inflammatory drugs (NSAID). The main mechanism of action include inhibition of the cyclooxygenase enzymes (COX).[8]

Paracetamol is one of the most popular and most commonly used analgesic and antipyretic drug around the world. It's available without a prescription, both in mono- and multi-component preparations.[9] It is a weak COX-1 and COX-2 inhibitor in the peripheral tissue with no significant anti-inflammatory effects.[8] Other possible mechanism include inhibition of COX-3 in the central nervous system (CNS) and modulation of serotonergic descending neuronal pathways, L-arginine/NO pathway and cannabinoid system.[9,10] It is most commonly administered orally 325 – 500 mg four times daily[8]. Dosing should not exceed 4 g/d, but for chronic use the dose can be limited to 2,5 g/d because of the higher risks for side effects.[11] The more recent availability of a preparation for IV infusion has increased its usefulness, especially in the perioperative settings[10]. Paracetamol is a hepatotoxic drug that can in lower doses cause a mild elevation of hepatic enzymes, but in doses higher than 4 g/d, especially with excessive alcohol consumption, serious hepatic damage can occur. [8,10] Liver failure can occur with a one-time ingestion of high doses of paracetamol (>12 g in an adult or 250 mg/kg in a child).[12]

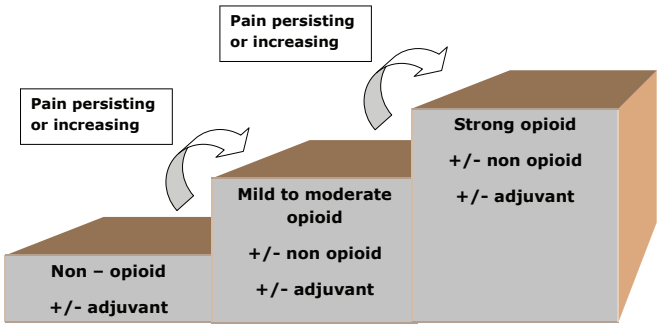
NSAIDs are a large group of medications that have antipyretic, analgesic and anti-inflammatory effects (table 1). All NSAIDs are essentially COX-2 inhibitors with a different degree of COX-1 inhibition that can be considered as a "side effect". Drugs that inhibit COX-1 and COX-2 with equal potency are known as nonselective COX inhibitors, while drugs with a intermediate or highly COX-2 selectivity are called selective COX-2 inibitors or ˝coxibs˝.[13] All NSAIDs have similar side effects that occur as a result of COX-1 inhibition. Prostaglandins (PG) regulate gastrointestinal (GI) blood flow and mucus secretion, exhibiting mucosal protective functions. By inhibiting PG production NSAIDs induce small intestinal injury.[14] Some NSAIDs can have different pharmacologic effects depending on the dose. Asprin (acetylsalicylic acid) has only anti-aggregatic effects on the thrombocytes in lower doses (40-80 mg/d), but in higher doses higher it has an anti-inflammatory effects (1g every 4-6 hours).[15]

Selective COX-2 inhibitors have less GI side effects and inhibit the COX-2 enzyme more effectively than non selective COX inhibitors, but at higher doses have an increased cardiovascular risk and should only be taken for a short period.[8,13]

Opioid analgesics

Opioid analgesic bind to specific G-protein coupled receptors (μ, δ, and ϰ) in the CNS wich are involved into the transmission and modulation of pain. Their complex mechanism include inhibition of voltage gated presynaptic Ca2+- channels, opening of K+-channels and inhibition of adenilat cyclase. Opioids are known for many dose dependent side effects like euphoria, sedation, respiratory depression, miosis, truncal rigidity, nausea, vomiting, cough suppression, constipation, hypotension, antidiuresis and bradycardia.[6,8]

Opioid drugs can be divided into strong agonists and mild to moderate agonists (table 2). They can be administered per os, parenteral, intravenous, transdermal and as a spinal opioid therapy. The oral route of administration should always be the first choice (codeine, oxycodone, hydrocodone). The usage of transdermal patches is appropriate in the setting of continuous pain in patients who cannot use the oral route of administration (terminal illness). In opioid-naive patients, opioids should be started at a low dose



and titrated slowly, to minimize risk of opioid related side effects. Long-acting opioids could provide more consistent control of pain and a lower risk of addiction or abuse.[16,17]

Tramadol is a weak μ – receptor agonist and a norepinephrine and serotonin reuptake inhibitor. It's effective in the treatment of mild to moderate pain, but is less effective for severe and chronic pain. The recommended dosage is 50–100 mg orally four times daily.[8,15] Tramadol is more appropriate than NSAIDs for patients suffering from gastrointestinal and renal problems. It is considered as a safer drug than other opioids because respiratory depression, cardiovascular side effects, drug abuse and dependence are less frequent.[18]

Ketamine is a phenylpiperidine derivative and a weak opioid receptor agonist. Most of its effect is achieved through the inhibition of N-methyl-D-aspartate (NMDA) receptors, but it also interacts with the muscarinic and monoaminergic receptors. Ketamine is often administered together with opioid analgesics, post-operatively and in the treatment of chronic cancer pain. It acts synergistically with opioids and improves their efficiency. Recent evidence show that ketamine has potent antidepressant qualities and produces almost immediate antidepressant effects (within 1 hour). Ketamine has psychedelic side effects that limit its clinical use.[19]

Conclusion

Pharmacotherapy of pain is a complex problem in the everyday practice of physicians. Successful treatment of pain requires a good knowledge of the pharmacokinetics and pharmacodynamics. A good cooperation with the patient is required in order to avoid misunderstanding about the proper drug dosing. It is also important to spot the possible side effects on time and to avoid adverse interactions with other medications. Additional caution is required in the application of opioid analgesics because of the possible development of tolerance and dependence.

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Farmakološko liječenje boli

SAŽETAK: Bol je neugodno osjetno i osjećajno iskustvo povezano s pravom ili potencijalnom ozljedom tkiva. Dok akutna bol ima svoju fiziološku ulogu u upozoravanju osobe o nekom patološkom zbivanju, kronična bol je izgubila tu ulogu. Kronična se bol povezuje i s nekim komorbiditetima i s lošijom kvalitetom života. Na temelju dostupnih algoritmima za liječenje boli, farmakoterapija treba početi s primjenom nesteroidnih protuupalnih lijekova. U koliko bol perzistira ili se pogoršava potrebno je u terapiju uključiti opioidne analgetike. Treba započeti s najmanjom mogućom dozom i koristiti u što kraće mogućem razdoblju kako bi se izbjegla pojava neželjenih nuspojava. Za uspješnu terapiju boli potrebno je dobro poznavanje farmakokinetike i farmakodinamike lijekova korištenih u terapiji.

KLJUČNE RIJEČI: farmakoterapija, kronična bol, NSAID, opioidi