REVIEW Libri Oncol., Vol. 37 (2009), No 1-3, 43 – 46

VARIABILITY IN THE RESPONSE TO OPIOID THERAPY

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Summary

Opioids are main drugs for the treatment of moderate and severe pain. Successful opioid treatment depends on achieving a favorable balance between analgesia and adverse effects. The effective opioid dose and adverse events may vary greatly across patients. Opioid analgesic efficacy is not always sustained during continuous and long term treatment. Decreased opioid analgesic efficacy could be the main problem, which can potentially arise from multiple mechanisms. Decreased opioid analgesic efficacy can be the result of opioid tolerance, opioid–induced hyperalgesia, psychological factors and advancement of the disease. The mechanisms involved in variability in the response to opioid therapy could be the result of changes in drug pharmacology and interactions or changes in nociception because of adaptive changes and genetic constellation and mutation. It is important to distinguish the clinical manifestations of decreased opioid efficacy which differ in their mechanisms and the efforts to assure treatment efficacy.

KEYWORDS: *opioid efficacy, quality of pain, adaptive nociceptive changes, genetic factors, drug interactions*

NESTALNOST U ODGOVORU NA TERAPIJU OPIOIDIMA

Sažetak

Opioidi su glavni lijekovi za liječenje umjerene i jake boli. Uspjeh liječenja opiodima ovisi o postizanju ravnoteže između analgezije i neželjenih učinaka. Učinkovitost doze opioida i neželjene pojave mogu jako varirati od bolesnika do bolesnika. Analgetsku učinkovitost opioida nije uvijek moguće održati tijekom neprekidnog i dugotrajnog liječenja. Glavni bi Potencijalni uzrok smanjenoj analgetskoj učinkovitosti opioida nalazimo u različitim mehanizmima. Smanjena analgetska učinkovitost opioida može biti rezultat tolerancije na opioide, hiperalgezije izazvane opioidima, psiholoških čimbenika i napredovanje bolesti. Mehanizmi koji utječu na nestalnost u odgovoru na terapiju opiodima mogu biti rezultat promjena u nocicepciji prouzročenoj adaptivnim promjenama te genetskom konstelacijom i mutacijom. Važno je prepoznati kliničke manifestacije smanjene učinkovitosti opioida koje se razlikuju s obzirom na mehanizme koji su ih pokrenuli te nastojati osigurati djelotvorno liječenje.

KLJUČNE RIJEČI: *učinkovitost opioida, kvaliteta boli, adaptivne promjene nociceptivnog sustava, genetski čimbenici, interakcije lijekova*

INTRODUCTION

The most common reason for moderate to severe pain is cancer. Pain is the first symptom of cancer in 20-50% of all cancer patients, and 75-90% of advanced or terminal cancer patient cope with pain of different origin and in different body locations. As well the pain could be of different quality and intensity. Untreated pain has deleterious effect to the patients and their families and should be treated effectively. Opioids are the main drugs in the treatment of cancer pain. The patients differ in the need of opioid dosage for effective pain alleviation as well as in the appearance of opioid

adverse events. The variability in the response to opioid therapy arises in different pain quality, adaptive changes in the nociceptive system because of opioid use, drug interactions and genetic factors. The diminished effect of opioids to neuropathic pain is well established as well as many drug interactions. Adaptive changes in nociceptive system and genetic factors are not so well known and still are under research. The known data on this issue help us to understand and cure such situations in an effort to assure treatment efficacy to the suffering pain patients.

PAIN QUALITY AND THE VARIABILITY IN THE RESPONSE TO OPIOIDS

The component of neuropathic pain is present in 40% of cancer patients. Neuropathic pain could be the consequence of cancer itself, chemotherapy or other reasons which are not connected with cancer. Neuropathic pain of cancer origin is usually caused with tumor compression or infiltration to nervous structures. Radiotherapy could cause fibrosis and mielopathy. Chemotherapy usually causes polineuropathies. In the algorithm for neuropathic pain treatment the first drug of choice are antidepresives and anticonvulsivs. Opioids are known as less effective in the treatment of neuropathic pain and that is the reason that they are the second class drugs in the algorithm for neuropathic pain treatment. In cancer patients opioids remain the first medicine even when they have the component of neuropathic pain. They are combined with other drugs for neuropathic pain treatment as needed (1).

ADAPTIVE CHANGES IN THE NOCICEPTIVE SYSTEM AND THE VARIABILITY IN THE RESPONSE TO OPIOIDS

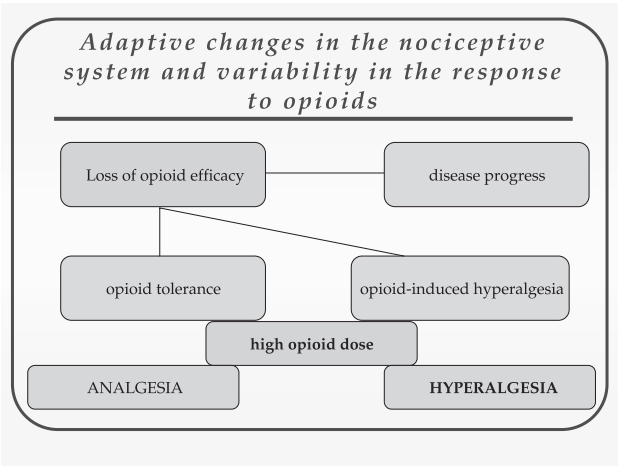
Sustained opioid administration could induce neuroplastic adaptations typically expressed as tolerance and opioid-induced hyperalgesia. The states are the result of opioid receptor (OR) and intracellular changes and are manifested as decreased analgesic efficacy or pain worsening. It is very important to distinguish opioid tolerance and opioid hyperalgesia and these conditions from physical and psychological addiction, pseudoadiction and opioid abuse. Exposure to the opioids can result in the development of tolerance which is expressed as a need to increase the dose of opioid over time to maintain a desired effect. The mechanism of tolerance is OR desensitization and changes in their internalization.

The direct result of opioid therapy may be opioid-induced hyperalgesia (OIH); patients become more sensitive to pain and have aggravation of their preexisting pain during opioid dose escalation. The mechanisms of OIH are desensitization, more powerful pronociceptive opioid effect, decreased descendent control of pain, and facilitation of nociceptive input in spinal and supraspinal nociceptive pathways.

Opioids may express antinociceptive and pronociceptive effect. Expression of the antinociceptive effect results in analgesia while expression of the pronociceptive effect results in hyperalgesia. The pronociceptive effect is longer in duration than the antinociceptive effect and that may result in withdrawal symptoms when opioids are abolished rapidly. Hyperalgesia could be a problem during opioid treatment. Mechanisms of OIH are of different origin than the mechanisms of opioid tolerance. These adverse effects of opioid treatment should be distinguished in clinical practice because of different approach of further analgesic therapy. In OIH involved are different mechanisms in the peripheral and central nervous system which cause the sensitization of pronociceptive pain pathways. The exact molecular mechanisms of OIH are not known completely but involve acute OR desensitization, increased activity of cAMP and endogenous dynorphin, increased production of excitatory neurotransmitters and descendent facilitation, and NMDA receptor activation (2-4). The appearance of OIH is not influenced with the mode of opioid use and could appear during systemic, peripheral or spinal opioid application (5). Opioids differ among themselves in the potential of producing OIH.

OIH could be proven with the methods of direct pain sensitivity assessment. The quality of pain in OIH is different from previous patients pain, clinically is similar to the neuropathic pain. The recognition of OIH is essential for further pain treatment (Table 1). The treatment involves the subsequent decrease of opioid dosing, the use of other methods of multimodal analgesia and opioid rotation. In multimodal analgesia all non-opi-

Table 1.
DIFFERENCE BETWEEN OPIOID TOLERANCE AND OPIOID-INDUCED HYPERALGESIA.



oid groups of analgesics are used, especially the antagonists of NMDA receptors. Systemic and regional analgesic techniques could be used.

GENETIC FACTORS AND THE VARIABILITY IN THE RESPONSE TO OPIOIDS

The opioid effect depends on pharmacokinetics and pharmacodynamics of the drug such as absorption, distribution, metabolism, and excretion and intrinsic efficacy at OR. Transporting proteins, metabolic enzymes, and many other transmitters are involved in these processes. Most of them are products under genetic control of their production and function. In the case of altered genetic control their production and function could be changed resulting in diminished opioid efficacy.

Pharmacogenetic research of drug metabolism and pharmacogenomic development of drugs became possible after human genome discovery in year 2001. The most frequent form of genetic differences among the patients is a single nucleotide polymorphism (SNP). SNP could influence individual reaction to disease, drugs and opioid effect, and environmental influences (6).

Variability in the response to opioids could be a result of genetic polymorphism in the opioid transporting proteins or the enzymes for opioid metabolism (7, 8). P-gicoprotein (p-gp group) is involved in opioid transport to OR. Mutation of the ABCB1 gene from the ABC family influences the response to morphine and methadone.

The main site for opioid action is μOR which is regulated with the OPRM1 gene. Patients with a 118G allele have weaker response to morphine. Mutation of the melanocortin receptor 1 gene (MC1R) is responsible for greater sensibility to pain stimulus.

Cytochrom P450 (CYP) is involved in the opioid metabolism. Mutation of CYP2D6 influences the analgesic effect of codeine and tramadol. Poor metabolizers have diminished the effect of these opioids.

Cathecolamine-O-methyltranspherase (COMT) is the main enzyme for cathecholamine. Polymorphism in the genes of this enzyme enhances the effect of morphine.

DRUG INTERACTIONS AND THE VARIABILITY IN THE RESPONSE TO OPIOIDS

Interactions among opioids and other drugs can mimic gene polymorphism. Usually, the interactions are the result of using the same transporting proteins and their subsequent lack; as well they may be the result of use of the same metabolic pathways and enzymes. Such interactions may be among codeine, oxycodone and tramadol and drugs such as tricyclic antidepresives, antipsychotics, antiarhitmics, antiemetics and amphetamine. The result is reduction of analgesia.

CONCLUSION

Effective pain and other symptoms alleviation are very important in the treatment of cancer patients. Opioids are recommended for the treatment of moderate to severe pain, but several barriers can limit the effective treatment. Variability to opioid therapy has different reasons. Most of the reasons could be found out and eliminated. Critical for the effective management of cancer pain is an appropriate knowledge of opioid pharmacology, clinical use, side effects and drug interactions. It is crucial to distinguish tolerance to opioids from OIH. Pharmacogenetic researches are giving us possibility to understand genetic variability to opioids and are opening new possibilities to use the most appropriate opioid to each patient.

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