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Adverse effects of opioid analgesics from the central nervous system

Abstract

Opioid analgesic drugs are widely used in the treatment of moderate to severe pain as well as symptomatic treatment of dyspnoea. However, the use of opioids may cause central adverse effects, such as delirium, cognitive impairment, sedation, hallucinations, myocloni, seizures, hyperalgesia, sleep and mood disorders. The ability to diagnose and properly manage the above adverse effects is important for the proper treatment of patients receiving opioid analgesics.

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Key words: hyperalgesia, delirium, opioid analgesic drugs, adverse effects, neurotoxicity

Introduction

Opioid analgesic drugs are widely used and constitute the primary method of treatment of moderate to severe pain. They are used in both short- and long-term treatment of pain of various aetiology. The main mechanism of opioid activity is the activation of receptors μ, κ i δ, which are located within the central nervous system (CNS), but can also affect other systems: serotoninergic, noradrenergic, dopaminergic, gabaergic and glutaminergic [1, 2]. Due to their mechanisms of action, many adverse effects of opioids involve the CNS.

Opioid neurotoxicity

Neurotoxic activity of opioids includes delirium, cognitive impairment, sedation, hallucinations, myocloni, seizures and hyperalgesia. The phenomenon is probably associated with the downregulation of opioid receptors and excessive activation of NMDA, N-metyl-D-aspartate receptors. The neurotoxic activity of opioids is most often caused by active metabolites of morphine, pethidine and hydromorphone, more rarely — oxycodone, tramadol, codeine and dihydrocodeine. Patients with renal failure, in whom toxic metabolites may be accumulated, are at a particular risk of opioid neurotoxicity. Opioids which appear to be safer in this regard are fentanyl and methadone, whose metabolism does not cause the synthesis of active metabolites, and buprenorphine, whose metabolites do not show neurotoxic effects [3].

In a study involving 600 patients under palliative care symptoms of neurotoxicity were observed in 57 (15%) patients. One symptom was observed 44% of the patients, and two or more symptoms were

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Table 1. Treatment of adverse effects of opioid analgesics from the central nervous system

Symptoms	Treatment methods
Excited delirium	Elimination of other causes of delirium, opioid rotation, antipsychotics
Cognitive dysfunction	Change or reduction of opioid dose, psychostimulants in selected patients
Sedation	Dose reduction, change of route of administration or opioid rotation, psychostimulants (modafinil and methylphenidate) in selected patients, donepezil
Hallucinations	Change of route of administration/dose reduction or opioid rotation/discontinuation, antipsychotics
Myoclonus	Opioid rotation or discontinuation, benzodiazepines or baclofen
Seizure episodes	Benzodiazepines
Hyperalgesia	Opioid dose reduction or opioid rotation, especially switching to methadone or buprenorphine; ketamine, propofol, COX-2 inhibitors, TCA, SNRIs, gabapentinoids, magnesium sulphate, alpha-2 agonists, valproic acid
Sleep disorders	Opioid dose reduction or opioid discontinuation; AVS in sleep-related breathing disorders
Nausea and vomiting	Change of route of administration or opioid rotation; antiemetics

observed in 56% of them. Patients who developed more symptoms were treated with higher doses of opioids. Symptoms of neurotoxicity were caused by hydromorphone (16 patients), morphine (13), oxycodone (11), fentanyl (10), hydrocodone (2) and drug combinations (2 patients). The most frequently reported symptoms included delirium (47%), sedation (42%), hallucinations (40%) and myocloni (37%) [3]. Symptoms of neurotoxicity depend on the dose, duration of treatment, plasma creatinine level, age and diagnosis of malignancy (Table 1).

Delirium

Delirium is the most often observed form of a neurotoxic effect of opioids that involves disturbance of consciousness and cognitive impairment, especially the ability to focus, sustain or shift attention. It develops rapidly and the severity of its symptoms varies throughout the day. It is accompanied by changes in motor activity — from hypokinesis to agitation, impaired perception and sleep. Delirium is associated with a longer time of hospitalization, increased treatment costs, higher frequency of re-hospitalization, deterioration in independent functioning and the risk of such adverse effects as removal of catheter, insertions and aggression. Delirium is also associated with a greater risk of death. The risk of death in a given year is 1.5 higher in patients with delirium hospitalized in geriatric units. The risk of death is 2–4 times higher in patients with delirium treated at ICU, and the risk of death within 6 months is 5 times higher in patients under palliative care [5].

The risk of delirium increases during opioid treatment [6–8], it occurs in 5–50% of elderly patients after surgical procedures [9] and in 28–44% of patients at the admission to palliative care facilities as well as in 68–88% of patients in the final days of life [6 ,7]. Opioids were a significant factor causing excited delirium in 21% of patients treated with them [7].

Mechanisms of delirium include dopaminergic and cholinergic dysregulation — increased activity of dopaminergic neurons with decreased activity of cholinergic neurons. Morphine, pethidine and tramadol have an antagonistic effect on muscarinic receptors. Moreover, administration of acetylcholinesterase inhibitors decreases the intensity of delirium [10–12]. Another possible mechanism is the direct neurotoxic effect of opioids or their metabolites [3].

In a systematic review, the use of pethidine was associated with a significant risk of delirium [11]. Pethidine increases the risk of delirium and is not recommended for pain treatment [13]. Other opioids associated with episodes of delirium are tramadol, morphine as well as the combination of morphine and oxycodone [11]. There are also reports of the occurrence of delirium during sublingual [14] and transdermal [15] treatment with buprenorphine as well as after adding methadone to oxycodone treatment [16]. Benitez-Rosario described cases of delirium caused by transdermal administration of fentanyl [17]. All opioids are associated with the risk of delirium, with pethidine posing the greatest, and oxycodone — the lowest. In a retrospective assessment of adverse effects of tapentadol, there were 244 cases of delirium per 18,028 cases of adverse effects [18].

In the treatment of delirium it is important to eliminate such causes as electrolyte and metabolic disturbances, dehydration, endocrinopathies, infections and other drugs, especially with cholinolytic effects and benzodiazepines, which may cause delirium [19]. Opioid rotation may be effective, and reduction in the intensity of the symptoms can also be obtained after

switching morphine to oxycodone [6], transdermally and parenterally administered fentanyl [20] as well as intravenously administered methadone [21]. There are reports describing an effective change of transdermally administered fentanyl to orally administered methadone [17]. Symptomatic treatment can also include antipsychotics [19].

Cognitive dysfunction

Cognitive functions can be defined as the ability to collect, store and re-enact information. Cognitive decline may have a significant negative impact on patients' quality of life, making it difficult to perform daily activities. It is also the most frequent reason for discontinuation of opioid treatment by patients [22].

Studies on healthy volunteers receiving opioids have shown that parenteral route of administration and higher doses were associated with cognitive decline. In cancer patients treated with opioids due to chronic pain, cognitive decline was associated with an increased dose of opioids. Patients receiving opioids had worse results in respect of operational memory, focus and alertness. Higher plasma concentration of the opioid was associated with worse results [22, 23]. Pethidine, morphine and hydromorphone were most often associated with cognitive symptoms [22]. While conducting treatment, physicians should consider dose reduction, change (rotation) or changing the route of opioid administration [22]. In some patients, psychostimulants such as modafinil (not available in Poland) and methylphenidate may be effective, however, they should not be routinely used due to their adverse effects and risk of drug interactions in patients requiring polypharmacy [12, 22].

Sedation

Sedation is a frequent adverse effect that occurs after the beginning of treatment or an increase in the dose of opioid analgesics. Although most patients develop tolerance to this adverse effect within several days, in some it may persist [22]. Sedation is most likely caused by the neurotoxic activity of opioids [3, 22]. Treatment includes dose reduction as well as change (rotation) of opioids. Although psychostimulants (modafinil and methylphenidate) may be effective in some patients, they are rarely recommended due to the above-provided reasons. Donezepil has also been proven to be effective [22–24].

Hallucinations

Hallucinations are one of the neurotoxic effects of opioids. Most of the described cases of hallucinations involve the use of morphine, other pethidine, hydromorphone, fentanyl, tramadol, buprenorphine, methadone and oxycodone. A drug safety study analysed reports concerning adverse effects of opioids in the years 1985–2015 — 482 out of 12,184 patients taking opioids reported hallucinations [25].

In Bruera's study, 4 out of 55 cancer patients with chronic pain experienced hallucinations after hydromorphone administration. Caraceni described 9 cases of morphine-induced hallucinations in a group of 161 cancer patients with chronic pain. Woodhouse described 6 cases of fentanyl-induced hallucinations in a group of 82 patients with postoperative pain [25]. In a retrospective analysis of 18,028 cases of adverse effects of tapentadol, 366 cases of hallucinations were reported [18].

Dysregulation of the dopaminergic system is one of proposed mechanisms of opioid-induced hallucinations. Animal studies point to the existence of opioid receptors in the ventral tegmental area — one of the dopaminergic centres in the brain. These receptors are located primarily on GABA (gamma-amino butyric acid) interneurons, which normally inhibit dopamine release. Dopaminergic neurons are disinhibited in the presence of opioids. Another proposed mechanism is direct neurotoxicity of some opioids and their metabolites, especially morphine, hydromorphone and pethidine [3]. Hallucinations may be an element of delirium or they may occur alone. The most common forms of opioid-induced hallucinations are visual or auditory hallucinations, which may take the form of musical hallucinations. Hallucinations usually occur within a few days of initiating opioid treatment or increasing the dose. They are continuous, depending on the plasma concentration of the opioid. Their duration varies, depending on drug metabolism and elimination [25].

The most effective treatment is discontinuation of opioid therapy, although it is associated with the risk of withdrawal symptoms and increased pain [2]. If that is not possible, the following procedures should be considered: dose reduction, dosage regimen change while maintaining the daily dose, opioid rotation. Antipsychotics can be used for treatment; haloperidol reduces the severity of hallucinations, however, second-generation drugs are preferred due to their more favourable side-effect profile [25].

Myoclonus

Myoclonus is a fairly common neurotoxic effect of opioid analgesics. Its risk increases during chronic treatment and high-dose opioid use, spinal cord injury (SCI), as well as concomitant administration of antidepressants, antipsychotics, antiemetics and nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 12, 26]. Its occurrence was described during tre-

atment with morphine, hydromorphone, hydrocodone, pethidine, methadone, fentanyl and tramadol. Most of the described cases involve intrathecal and intravenous administration of opioids; descriptions of myoclonus after orally administered opioids are less frequent [3, 12, 27–30]. Possible mechanisms of myoclonus include neurotoxic effects of opioids and their metabolites, inhibition of GABA neuronal activity and disinhibition of dopaminergic neurons [3, 12]. Treatment consists of therapy discontinuation or opioid rotation [3]; benzodiazepine drugs or baclofen may be used symptomatically [24].

Seizures

Seizures are rare adverse effects of opioid analgesics. Most studies and case reports involve intrathecal administration of morphine, parenteral administration of hydromorphone and oral administration of tramadol. The frequency of seizures correlates with the dose and plasma concentration of the opioid. Tonic-clonic seizures are the most common [31–34]. In the case of tramadol, seizures were observed in 38% of poisonings, in 37% of patients abusing the drug and in 3% of patients taking therapeutic doses [31]. The mechanisms of opioid-induced seizures include an inhibitory effect on GABA neurons, excitatory effects of active metabolites on NMDA receptors, a direct effect on μ receptors located on astrocytes and, in the case of tramadol, inhibition of serotonin and norepinephrine reuptake [31, 34]. Benzodiazepine drugs may be used for treatment of seizures. Patients were described in whom tramadol-induced and morphine-induced seizures resolved after naloxone administration. Due to conflicting results concerning the effectiveness of this treatment, the administration of the above-mentioned drugs it is not recommended [31, 32].

Opioid-induced hyperalgesia

Opioid-induced hyperalgesia (OIH) is a pain threshold reduction under the influence of opioid *analgesics*. It is a phenomenon that needs to be differentiated from analgesic tolerance – both phenomena are associated with an increase in pain during treatment with opioid analgesics, which is unrelated to progression of the underlying disease. In the case of analgesic tolerance, a 30-50% increase in the drug dose is usually related to the level of analgesia similar to that before the development of this tolerance. Such a procedure, however, may exacerbate pain in case of the occurrence of OIH, as dose escalation is related to increased nociception and the occurrence of adverse CNS changes that exacerbate pain perception. Failure to diagnose OIH may be related to irrational escalation of opioid doses to reduce pain intensity, resulting in paradoxical exacerbation of pain. OIH can also be diagnosed when there is a change in pain phenotype during opioid treatment. This abnormally increased sensitivity to pain occurs in regions where it was not previously present. In a short period of time there is a change in the nature of pain, or there is allodynia [35].

The following elements play an important role in the OIH pathogenesis: genetic and epigenetic factors, changes in opioid receptor sensitivity, an increase in spinal dynorphins (especially after intravenous opioid administration) and excitatory neuropeptides, modifications in alpha-2 autoreceptor reactivity, descending inhibitory malfunction, changes in on- and off-cells in the brainstem, increased levels of calcitonin gene-related peptide (CGRP) and substance P (SP) in dorsal root ganglia (DRG). From a clinical perspective, the most relevant role is that of NMDA receptor activation, which is related to increased release of pro-nociceptors and apoptosis of dorsal horn cells of the spinal cord [35, 36].

Therapeutic strategies include either dose reduction or opioid rotation, or the use of other drugs: ketamine, propofol, cyclooxygenase 2 (COX-2) inhibitors, alpha-2 receptor agonists (clonidine, dexmedetomidine), valproic acid, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), gabapentin, pregabalin and intravenous magnesium sulphate. The first of the listed treatment options may be related to the risk of withdrawal symptoms and an increase in pain intensity. In such case, it may be necessary to administer adjuvant analgesics, e.g. SNRI, TCA, gabapentinoids. Changing the opioid is aimed at providing effective analgesic effect with greater tolerance and lower neurotoxicity. In this case, it may be particularly beneficial to administer methadone, which is an NMDA antagonist, as well as buprenorphine, whose antagonism against the receptor κ may inhibit the pronociceptive activity of dynorphin within the spinal cord [35]. Elements of OIH prevention are also important. They include personalized selection of an opioid analgesic, dose titration, administration of opioids in combination therapy with other drugs enabling lowering of the opioid dose while maintaining effective analgesia, with simulate nous prevention of OIH [35, 36].

Sleep disorders

Sleep disorders are a common problem occurring in 75% of patients treated with opioids, and they may increase the risk of cognitive impairment, mood disorders and decreased pain tolerance [37]. In polysomnographic studies of long-term, opioid-treated patients, the most common findings include reduction of stage N3 (deep sleep), prolongation of REM (rapid

eye movements) sleep latency, reduction of REM sleep latency , and a greater proportion of stage N2. A reduction in total sleep time was also observed in some patients [38]. Chronic opioid use is a risk factor for sleep-related breathing disorders, with an incidence of 30-90% in opioid-treated patients [39].

The evidence of disorders shows signs of obstructive sleep apnoea (*OSA*) and central sleep *apnoea* (CSA); it may include hypoxia, hypoventilation, hypercapnia and ataxic breathing. The intensity of symptoms is proportional to the opioid dose used [39]. Drug treatment options are limited and they include dose reduction or drug discontinuation if possible. The use of continuous positive *airway* pressure (CPAP) ventilation can reduce the severity of symptoms related to OSA, however, it is sometimes ineffective due to the presence of CSA, in which case treatment with adaptive support ventilation (ASV) may be effective [39].

Mood disorders

There is evidence of the relationship between opioid use and mood disorders. Epidemiological studies found the relationship between opioid use, beyond medical indications, and the risk of depression [40]. An increased risk of a first depressive episode was found during more than 90-day opioid treatment [41], as well as during administration of doses exceeding the equivalent dose of 50 mg of morphine [42]. Opioid use was also associated with a higher risk of depression relapse in individuals with a history of depressive disorders [43]. Importantly, the opioid use was a factor for depression, independent of the presence of chronic pain. In a study concerning the effect of opioids on the course of bipolar affective disorder, 6 patients out of 45 had a manic episode after opioid initiation and 3 patients had a hypomanic episode. Hydrocodone was administered in 7 patients, while morphine and tramadol in the remaining 2 patients [44]. There are also reports indicating pro-manic effects of tramadol administered both in monotherapy [45, 46] and in combination with selective serotonin reuptake inhibitors (SSRIs) and SNRIs [47, 48].

Nausea and vomiting

Opioid-induced nausea and vomiting (OINV) occur, respectively, in 40% and 15–25% of patients with chronic pain, who are treated with opioid analgesics [49]. Most patients quickly develop tolerance to OINV; however, some patients experience the above-mentioned symptoms chronically. The risk of OINV is proportional to the dose used and it is similar for most opioid analgesics. OINV may be accompanied by dizziness which may increase in severity when moving [50]. The pathophysiology of OINV is related to adverse CNS effects: activation of chemoreceptors in the fundus of the fourth ventricle, increased sensitivity of the labyrinth, as well as PNS effects of opioids on the gastrointestinal tract, described as opioid-induced bowel dysfunctions (OIBD) [50].

An opioid rotation can be taken into account during treatment — the effectiveness of switching morphine to oxycodone, tramadol to codeine or oxycodone, and morphine or oxycodone to methadone was described. The change of the route of opioid administration from oral to transdermal may reduce the intensity of nausea. Antiemetics, especially anti-dopaminie drugs (metoclopramide, haloperidol, thiethylperazine, olanzapine and other neuroleptics), antihistamines and serotonin 5-HT3 receptor antagonists may be effective [50].

Summary

Opioid analgesics may cause numerous adverse CNS effects, the incidence and severity of which are related to the pharmacodynamic and pharmacokinetic properties, treatment duration, route of administration and opioid dose, and individual patient characteristics. The occurrence of adverse CNS effects may impede appropriate pain management, limiting the dose escalation. It sometimes requires a change or discontinuation of opioid treatment and the use of other drug groups.

Declaration of conflict of interests

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