Artykuł poglądowy

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The use of opioids in the treatment of non-neoplastic pulmonary diseases

Zastosowanie analgetyków opioidowych w leczeniu objawowym pacjentów z rozpoznaniem zaawansowanych nienowotworowych chorób płuc

Abstract

Studies on the endogenous opioid system have demonstrated its presence, including opioid receptors, not only in the central nervous system but also in the respiratory tract. Although dyspnoea mechanisms are not fully understood, the presence of these receptors, both centrally and peripherally, provides the potential for treatment of respiratory symptoms, such as dyspnoea and cough, with systemic and local application of opioids, used when causal treatment of advanced non-cancer pulmonary diseases becomes insufficient. While quality of research supporting the use of opioids in the treatment of cough remains low, there is a growing body of evidence supporting the efficacy and safety of parenteral and nebulised opioids in the symptomatic treatment of dyspnoea.

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Key words: opioids, dyspnoea, cough, palliative care, lung disease

Streszczenie

Badania nad endogennym układem opioidowym wykazały obecność receptorów opioidowych, nie tylko w ośrodkowym układzie nerwowym, ale także w drogach oddechowych. Chociaż mechanizmy duszności nie są w pełni zrozumiałe, obecność tych receptorów, zarówno centralnie jak i obwodowo, zapewnia możliwość leczenia objawów ze strony dróg oddechowych, takich jak duszność i kaszel, przy ogólnoustrojowym lub miejscowym zastosowaniu opioidów, kiedy leczenie przyczynowe zaawansowanych nienowotworowych choroby płuc jest niewystarczające. Podczas gdy jakość badań dotyczących stosowania opioidów w leczeniu kaszlu pozostaje niska, istnieje coraz więcej dowodów potwierdzających skuteczność i bezpieczeństwo parenteralnych i nebulizowanych opioidów w leczeniu duszności.

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Słowa kluczowe: opioidy, duszność, kaszel, opieka paliatywna, choroba płuc

Introduction

Palliative care aims to improve quality of life (QoL) of patients and their families facing life-limiting, progressive diseases, by preventing and alleviating somatic, psychological, social and spiritual issues through their early identification, evaluation and treatment. It is widely recognised as an important

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part of the comprehensive care plan for patients with severe lung diseases. The most common symptom in this group of patients, and yet most difficult to treat, is intensifying dyspnoea, which develops in the natural course of many respiratory diseases. Moderate to severe dyspnoea appearing during minimal effort is experienced by over 90% of patients in advanced stages of chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF) [1]. Other common respiratory symptom, sometimes occurring along dyspnoea, is chronic cough. Chronic cough, i.e. lasting more than eight weeks, occurs frequently in advanced respiratory diseases [2] and has the ability to severely impact QoL as in IPF, where cough appears in 70–85% of patients, and is often severe enough to cause them to avoid social interactions in fear of incontinence, emesis or syncope [3]. It is to no surprise then, that patients with advanced pulmonary disease must be provided with a multidisciplinary care plan [4, 5], including effective pharmacotherapy.

Mechanism of action

To date, opioids are the only confirmed endogenous neurotransmitters, which modulate dyspnoea. It was demonstrated in several studies, that blocking opioid receptors with intravenous naloxone, which acts both in central nervous system and peripherally, increases dyspnoea in COPD [6, 7] and asthma patients [8], subjected to treadmill exercise [6], resisted load breathing [7] and methacholine provocation [8] without alteration in β-endorphin immunoreactivity in circulating blood [6, 7], oxygen uptake [6, 7], minute ventilation [6–8] and cardiorespiratory parameters [6, 7]. Opioid receptors are widely distributed throughout central nervous system, including the nociceptive system and respiratory centres in brainstem [9, 10]. In the receptor binding study of central nociceptive system, Baumgartner et al. [10] have shown that opioid receptors occur most densely in thalamus, basal ganglia, amygdala, cingulate cortex and insular cortex. Similar brain structures, i.e. insular cortex, anterior cingulate cortex and amygdala, have been shown in neuroimaging studies to be strongly involved in dyspnoea processing [11]. Von Leupoldt et al. [12], who compared dyspnoea and pain processing in the same group of participants, have shown, that both symptoms share same brain areas. However, being a part of limbic system, aforementioned brain structures might have been activated due to anxiety or fear caused by dyspnoea, rather than dyspnoea itself [11, 13]. Furthermore, most of neuroimaging studies were performed in small numbers of healthy volunteers, whose dyspnoea was triggered by various stimuli, including acute hypercapnia, which can alter cerebral blood flow, meaning that their results should be treated with caution [11, 13].

It is postulated, that opioids alleviate dyspnoea by decreasing respiratory drive, modulating central dyspnoea perception, decreasing anxiety and binding with peripheral opioid receptors in lung [14]. Opioids indeed can reduce the sensitivity of the brainstem respiratory centres to hypercapnia and hypoxia, thus promoting loss of respiratory drive, what might lead to higher pCO_2 and lower O_2 levels [9]. However, as demonstrated in metanalyses of randomised controlled trials (RCT) of opioid use in dyspnoea [15, 16], opioids can reduce dyspnoea in doses which do not cause significant changes in blood gases levels. In a study by Estfan et al. [17], parenteral administration of opioid for cancer pain management did not cause significant change in blood gas parameters or drop in respiratory rate (RR), except in two patients, out of thirty, whose RR drop was transient, did not cause hypoventilation and resolved spontaneously. However, in a study conducted by Clemens et al. [18], who delivered opioids to dyspnoeic palliative care patients, authors did observe drop in RR, following dyspnoea improvement after morphine application, which nonetheless did not change S_aO_2 and tcP-CO_2. The authors speculate, that it might be a result of a rise in tidal volume, which sustained minute ventilation, however, tidal volume was not measured. It is worth underlining, that anxiety was measured on numerical rating scale along with dyspnoea, and a significant correlation between the two was observed, meaning that drop in RR might have been a result of anxiety reduction. This drop, along with other, reduced physiological reactions to anxiety can translate into reduced O_2 consumption. It therefore comes as no surprise, because endogenous opioid system is essential to neural modulation of anxiety [19]. On the other hand, Pattinson et al. [9] emphasise, that even though opioids do cause reduction in hypercapnia ventilatory response, the change in steady-state pCO2 will be minor.

Opioids are also known to reduce air hunger [13], by modifying mismatch between actual ventilation, limited by pulmonary disease, and motor drive to breathe, which is relayed by corollary discharge to the cerebral cortex. It was demonstrated in neuroimaging studies [14], that opioids alter cerebral blood flow in aforementioned brain regions, presumably engaged in dyspnoea processing.

Opioid receptors can also be found in respiratory tract, although their local physiological role is uncertain. Animal studies showed, that opioid receptors are distributed in respiratory tract peripherally, mainly in

alveoli [20], however, this is not true for humans. Recent studies have shown, that human lungs have all the necessary components of endogenous opioid system, i.e. opioid peptides, their precursors, and appropriate proprotein convertases, with corresponding opioid receptors located densely in superficial layers of trachea and large bronchi on C-fibres and pulmonary neuroendocrine cells (PNEC) [21]. Human opioid receptors are also located on submucosal bronchial glands and alveolar macrophages [21]. Exact function of this local, pulmonary opioidergic system, along with PNECs, is unknown, however, it is postulated that it might participate in maintaining homeostasis of respiratory tract and that its elements can also be targeted to treat dyspnoea, specifically to modulate peripheral transmission via vagal afferents innervating bronchi [21, 22].

The antinociceptive effect of opioids associated with their action on μ, κ and δ receptors, located in the central nervous system (CNS) and in the peripheral tissues, can also be beneficial in dyspnoeic patients, whose breathing is limited or aggravated by pain [9], which is a common, accompanying symptom in advanced pulmonary diseases e.g. COPD [23]. On the other hand, alleviating pain in given patient might reveal full extent of opioids negative influence on respiration, previously stimulated by pain [9]. Opioid receptors can also affect cough reflex. Although cough is mediated by all subtypes of afferent nerves innervating the airways, including opioid receptor-rich C-fibres, antitussive opioids act mainly centrally, in brainstem cough centres [24].

Clinical practice guidelines and meta-analyses

The increasing knowledge of opioid receptors/systems in respiratory tract, and growing number of RCTs demonstrating the positive effect of opioids on respiratory symptoms are reflected in changing palliative treatment guidelines. Significant progress has been made in recognising opioids as complementary to disease-targeted treatment in advanced lung diseases, thus opioids are currently recommended in managing dyspnoea in advanced diseases of lung and heart by a significant number of national and international associations, including American College of Chest Physicians [25], Global Initiative For Chronic Obstructive Lung Diseases [26] and others [2, 27]. Before commencing the treatment, patients should measure their dyspnoea on an appropriate scale, such as visual analogue scale or numerical rating scale [2, 25]. Dyspnoea intensity should then be regularly reviewed during the treatment to assess its effectiveness. Apart from pharmacotherapy, patients should also be advised on other, non-pharmacologic therapies of proven efficacy, such as pursed–lip breathing, handheld fans, chest wall vibration, neuromuscular electrical stimulation or relaxation [2, 25, 27]. It is prudent to exclude other, potentially treatable co–morbidities, such as heart failure or gastro-oesophageal reflux, which might increase dyspnoea in patients with advanced lung diseases. Moreover, it is essential to discuss the end-of-life care with patients, explaining its role and its limits [25]. Opioids are also recommended in treatment of cough, although quality of evidence, including cancer–related cough, is low [28].

Recommendations of Association for Palliative Medicine of Great Britain and Ireland [29] and meta-analysis conducted by Yancy et al. [30], both, despite low-quality evidence, point to opioids as one of the options in the treatment of cough in malignant and non-malignant diseases. However, according to guidelines [3, 29, 31, 32], opioid treatment trial should be proceeded with careful differential diagnosis regarding other causes of cough, which could be treated causally e.g. gastro-oesophageal reflux, rhinosinusitis or ACE inhibitors. Afterwards, a trial with medications with more favourable side-effects profile compared to opioids should be conducted, which include demulcents, expectorants or sodium cromoglicate inhalations [29, 32]. When this approach fails, opioids or opioid derivatives, such as dextromethorphan, could be started [29, 32]. Other pharmacotherapy options include substances, which suppress cough centrally e.g. butamirate, gabapentin, amitriptyline; or peripherally, through their action on afferent nerves e.g. levodropropizine, nebulised lidocaine or thalidomide [3, 29, 32].

Opioids can be delivered systemically — most commonly orally [33]. While all opioids used for respiratory indications can be administered orally, some of them, i.e. morphine, oxycodone, fentanyl, can be delivered subcutaneously. These opioids can also be used intravenously, when there is a need for a fast onset of action or when there are contraindications to oral or subcutaneous delivery i.e. generalised oedema, anasarca, impaired peripheral circulation, coagulation disorders, rash or other skin changes, especially its infections, nausea, vomiting, and bowel obstruction [34, 35]. It is important to modify the dosage accordingly when changing route of drug delivery.

Other therapeutic option is delivering opioids through nebulisation, which seems to be a preferred route of drug administration by most palliative patients with dyspnoea [35]. Treatment of respiratory disorders by delivering drugs locally, via inhalations, is common because of its advantages, which include achieving high

drug concentrations locally with little systemic impact. However, there is no consensus among researchers whether nebulised opioids act locally, through their receptors on PNEC and C–fibres, or systemically, after absorption from airways [36]. It is worth underlining, that systemic absorption of nebulised morphine, delivered by jet nebulisers, is low, approximately 5% [37, 38]. Bioavailability of lipophilic fentanyl, encapsulated in liposomes, delivered by jet nebuliser is slightly higher — 12% [39]. It is possible to increase bioavailability of nebulised opioids even further, to nearly 100%, by using novel nebulisers targeting pulmonary alveoli, both with morphine and fentanyl [40, 41]. However, this kind of drug delivery does not differ significantly from intravenous route and shares similar side effects profile, significantly more burdensome compared to opioids delivered to bronchial tree [16]. In vitro studies show that opioids, applied locally, can reduce mucus production, limit bronchus constriction and release of pro-inflammatory mediators [20, 21], suggesting their role in maintaining pulmonary homeostasis. It is to no surprise when it is postulated that opioids, through the interaction with their respective receptors on PNEC and innervating them C-fibres, might limit neurogenic inflammation and signal generation to CNS [21]. These claims seem to be supported by the study of Quigley et al. [42], in which adding nebulised morphine to systemic morphine, further decreased dyspnoea intensity in cancer patients.

Clinical efficacy of nebulised opioids in dyspnoea treatment, most often morphine [43–61], hydromorphone [55, 57, 62, 63] and fentanyl [36, 64, 65], was studied in different patient populations, i.e. with primary or metastatic lung cancer [43, 45, 46, 54–57, 60, 63, 65], COPD [36, 46, 51, 52], ILD [46, 48, 51, 52] and CF [58, 59, 64]. Research, however, is inconclusive so far. Although initial, low level evidence studies suggested their positive effect on dyspnoea, three meta-analyses of RCTs [16, 66, 67] did not support this notion, thus treating dyspnoea with nebulised opioids remain unsupported by national and international respiratory guidelines [2, 25, 27]. Merely one meta–analysis demonstrated positive effect of nebulised opioids in treating dyspnoea [15], although this was thanks to one RCT [53]. However, there are doubts whether jet nebulisers used in studies so far, calibrated mostly for peripheral deposition, were appropriate for delivering morphine to respiratory tract. Recently, Janowiak et al. [68] published results of a RCT, in which morphine was delivered by dosimetric nebuliser, calibrated to target large airways, where most of the human opioid receptors are located on PNEC and C-fibres, which allowed to achieve a significant dyspnoea reduction. Nebulised morphine was also employed to treat persistent cough, however, its positive effect was reported in case studies [69–71] and was not verified in RCTs.

Characteristics of selected opioids

According to a Cochrane systematic review, only two opioids, delivered systemically, are effective in treating dyspnoea: morphine and dihydrocodeine [67]. However, these drugs are not safe to use in patients with significant renal failure, that is why guidelines [2, 72] recommend in this group, a trial of opioids, whose metabolites do not accumulate in renal failure i.e. fentanyl, oxycodone, methadone or hydromorphone. However, apart from fentanyl [73–76], these substances were not thoroughly tested in this setting. Methadone for dyspnoea was studied only after epidural use [77], hydromorphone was ineffective [63], whereas oxycodone effectiveness was reported in case studies [78, 79]. Regarding cough treatment, according to the Cochrane systematic review [28], the most effective opioids are morphine, codeine and dihydrocodeine — however, the quality of evidence is low.

Opioids of step two analgesic ladder

Codeine is a methyl derivative of morphine, 5–10% of its dose is metabolised to morphine. Codeine has central antitussive activity, as well as weak sedative and analgesic effect through its action on μ receptors. Its antitussive and analgesic effect is maintained for four to six hours. The maximum dose is 240 mg per day, while interval between doses should be no less than four hours. It is worth underlining, though, that codeine, according to latest evidence, has no benefit over dextromethorphan or placebo in cough treatment and should be avoided [29, 31]. A low-dose, slow-release morphine should be tried instead [29].

Dihydrocodeine (DHC) — is a semi-synthetic opioid analgesic, derivative of codeine, formed by hydrogenation of double bonds in the main chain of the codeine molecule. Dihydrocodeine is used as an alternative to codeine in treating moderate to severe pain, dyspnoea, and cough. Its dosage is 60 to 90 mg q12h. Daily dose should not exceed 240 mg [34, 80].

Opioids of step three analgesic ladder

Morphine is a pure opioid receptor agonist, binds predominantly to μ receptors and, to a lesser extent, also to κ and δ receptors. After crossing the blood-brain barrier, morphine and its metabolites, deliver a strong analgesic and sedative effect, as well as cause

depression of respiratory and cough centres in the medulla. It is worth mentioning, that its antitussive effect occurs in lower doses than analgesic [29]. Due to its hydrophilic properties, morphine does not accumulate rapidly in CNS, what makes it theoretically safer than lipophilic opioids, such as fentanyl, especially in populations with a high risk of respiratory depression [9].

Morphine, delivered orally and parenterally, is the opioid of choice in the treatment of dyspnoea. It is also indicated in the management of pain, cough, dyspnoea and diarrhea. There is no uniform dosing schedule of morphine in patients with dyspnoea. However "start low and go slow" approach is recommended — mostly because of a lower risk of side effects. It is worth to emphasise, that sedation is usually not observed and there are no reports of respiratory depression, if careful morphine titration is instituted [2]. Guidelines propose the following morphine dose titration scheme in dyspnoea:

1. In opioid-naive patients the typical, initial oral dose of immediate-release morphine in non-cancer lung diseases is 1.25 to 2.5 mg q4h [2]. However, some experts recommend even lower doses of morphine. The Canadian Thoracic Society experts in COPD [27] guidelines propose to administer initially 0.5 mg immediate-release morphine syrup q12h. If no side-effects are observed for two days, the dosage should be increased then to 0.5 mg q4h, while awake, for five days. After that period, dosage can be increased to 1.0 mg orally q4h, while awake, and then increased weekly by 1 mg q4h or 25% of the current dose. This approach might allow for safer adaptation to lowered hypercapnia ventilatory response [9]. Other approach was presented by Currow et al., who, in a study on chronic dyspnoea [81], safely started patients on 10 mg daily of sustained-release morphine, increasing this dose weekly by 10 mg to a maximum dose of 30 mg daily. Study group included COPD, ILD, primary and metastatic cancer patients.
2. If dyspnoea develops in a patient previously treated with opioid other than morphine or dihydrocodeine, discontinuation of therapy and initiation of morphine in appropriate dose might be considered [72].
3. In a patient who has previously received morphine for pain and developed dyspnoea afterwards, an additional dose is required, usually 25–50% of the current daily dose, based on dyspnoea severity [2, 36].
4. When the lowest effective, stable, i.e. unchanged for at least two weeks, opioid dose, without significant side–effects is reached, immediate-release formulations can be changed to sustained-release. Typically, dyspnoeic patients achieve full benefit of opioid therapy while receiving 30 mg of morphine daily, or less [81]. It is worth underlining that tachyphylaxis has not been observed despite several months of use [81].
5. Rescue doses in episodes of sudden dyspnoea exacerbations i.e. breakthrough dyspnoea dose could range from 1/10 [72] to 1/6 [82] of the total 24-hour regular dose or equal 50% of q4h dose [2].

Oxycodone is a pure opioid agonist with affinity to μ, κ, and δ receptors, with analgesic and sedative effects. Starting dose in opioid-naive patients equals 10 mg q12h. Other indications for oxycodone, apart from dyspnoea, are moderate to severe pain and severe idiopathic restless leg syndrome [14, 83].

Fentanyl is a synthetic opioid analogue with a potency 100 times greater than morphine. It is characterised by a strong affinity to μ opioid receptors and a weak affinity to δ opioid receptors. Fentanyl is highly lipophilic and easily penetrates the blood-brain barrier, thus it acts rapidly. It accumulates in liver failure, however, is well tolerated in kidney failure. The most popular formulations are transdermal patches, buccal tablets, nasal spray and ampules for either intravenous or subcutaneous injections and subarachnoid or epidural infusion. Because of its properties, fentanyl has been shown to be useful in breakthrough dyspnoea [82], especially when delivered transmucosally or as nasal spray. Moreover, in a RCT by Simon et al. [76], fentanyl buccal tablet, 100–200 μg, provided greater and faster dyspnoea relief than immediate-release morphine.

Adverse effects of opioids

Although opioids delivered via nebulisation have limited side effects [16], of which most often reported are bitter taste [35–39], cough [44, 46] or dizziness [42], this is not the case for parenteral opioids. The most common side effects of parenteral opioids include nausea, vomiting, sedation, pruritus, hyperalgesia and constipation, which is the most frequent one [34]. Careful dose titration is essential in the prevention of undesirable effects. Furthermore, it is advisable to implement prevention measures simultaneously with opioid therapy [84], e.g. constipation should be prevented through proper diet, laxatives or treatment with opioid antagonists, e.g. prolonged-release tablets of oxycodone combined with naloxone [34].

Chronic opioid use can also worsen obstructive, as well as central sleep apnea and reduce CPAP efficacy [85]. These negative effects are especially evident, when patient is on methadone, opioid doses are high

(> 200 mg daily morphine equivalent dose), and when opioids are co–administered with benzodiazepines [86]. However, evidence is conflicting with some of the studies showing improved sleep quality with opioid use [86]. Nevertheless, once daily dosing, in the morning, as in the study conducted by Currow et al. [81], seems to have the least influence on sleep quality [87].

Two of the aforementioned opioids, i.e. morphine and codeine, can cause significant histamine release via mast cells degranulation, whereas histamine release by oxycodone and fentanyl is minimal [88]. Histamine release results in dilatation of blood vessels and, in some patients, might cause urticaria, pruritus and bronchospasm. Because of this, opioids, especially morphine and codeine, should be avoided in severe asthma, or if necessary should be used with caution, and their dose should be reduced when asthma exacerbation develops [89, 90]. It is worth to underline, that metanalyses of RCTs [15, 16], studying the use of parenteral and nebulised opioids in dyspnoea, did not report any bronchospasm incident or any other serious adverse effect.

Fear of respiratory depression associated with opioid use has previously prevented their use in oncology and is still feared by medical professionals [91–93]. Meanwhile, respiratory depression is a rare phenomenon, which occurs in 0.2% of patients [84] and is easily avoided by proper dose titration [81]. Moreover, respiratory depression in usually proceeded by change in mental status and sedation [17]. The risk of respiratory depression increases in the elderly, obese, in the patients with concomitant cardiac diseases [85], and when opioids are used together with other medications, which influence the respiratory centres in brainstem [9]. Although, as mentioned above, opioids can reduce dyspnoea without causing significant changes in blood gas levels [15, 16], there are still concerns whether patients with hypercapnia can be safely treated with opioids [27]. Ekstrom et al. [94] published a prospective study on 2249 COPD patients starting long-term oxygen therapy in Sweden and showed that treatment with low-dose opioids for dyspnoea, i.e. ≤ 30 mg daily [81] is not associated with higher mortality, even in patients with concurrent hypercapnia. Nevertheless, chronic opioid use in hypercapnic patients should be cautious and, possibly, associated with blood gas monitoring. However, most guidelines do not address this issue. It is worth mentioning, that in the aforementioned study [94] higher opioid doses, i.e. > 30 mg daily, were associated with higher mortality. Similar association between higher mortality and opioid use in COPD patients was also found in a retrospective study by Vozoris et al. [95]. However, the authors of other observational study [96], in general Norwegian population, suggest that this association is probably caused by greater opioid use in patients approaching death. Furthermore, retrospective studies conducted among patients at the end of life did not show that opioids shorten survival [97, 98].

Summary

The use of opioids in the treatment of advanced lung diseases is related to their analgesic and antitussive properties along with their direct effect on dyspnoea, both central and, presumably, local. The development of medical knowledge and growing clinical experience have especially affected dyspnoea treatment guidelines, which now recommend opioids as a standard, palliative measure, despite fear of side effects among healthcare professionals. The proper opioid treatment, i.e. choosing a proper drug, way of delivery and dose titration permits safe use of opioids in dyspnoea therapy. Opioids can be delivered via different routes: orally, subcutaneously, intravenously, intranasally, buccally and via nebulisations. The latter, despite controversies, if proven efficient in further studies, could be a viable route of opioid delivery because of its ease of use and limited side effects.

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