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Review article

Opioids for the treatment of dyspnoea in patients with chronic heart failure

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ABSTRACT

Dyspnoea is one of the main symptoms found in patients with chronic heart failure. The awareness of the fact that palliative symptomatic treatment is an important part of the comprehensive approach in the case of the gradual progression of a chronic disease has improved recently. Opioids seem to be suitable medicine for the symptomatic treatment of refractory dyspnoea in patients with advanced chronic heart failure. Randomized controlled clinical trials have proven that the administration of systemic opioids results in the attenuation of dyspnoea. The described mechanisms of the effects of opioids include a reduction in respiratory drive, a reduction in the central perception of dyspnoea, a reduction in the activity of peripheral opioid receptors in the airways and the remission of anxiety. A major obstacle to the use of opioids so far has been its various adverse effects, particularly the fear of respiratory centre depression. Considering the variable response to opioids-based treatment, it is necessary to individualize dosing, beginning with the lowest possible dose and increasing it gradually depending on the severity of the symptoms. In the future, additional clinical trials will have to be implemented to extend our knowledge and allow us to understand the role of opioids in the treatment of refractory dyspnoea.

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Introduction

Chronic heart failure is a serious disease associated with a high degree of morbidity and mortality [1]. Large-scale randomized clinical trials have proven the prognostic benefit of the pharmacological treatment of heart failure with ACE inhibitors, beta-blockers, aldosterone blockers or recently with sacubitril/valsartan-based treatments. These medicines have indisputably attenuated the disease symptoms, reduced the number of re-hospitalizations and improved the quality of patients' lives [2]. Regardless of the optimal pharmacological treatment, a high percentage of patients with heart failure suffer from refractory symptoms, such as dyspnoea, coughing or pain [1,3,4]. The idea that patients suffer from dyspnoea due to the retention of water in the organism is wrong. There are other mechanisms which are known to be specifically related to heart failure, such as changes in the ventilation/perfusion ratio, myocardial ischaemia or atrophy of skeletal muscles [5].

From the point of view of morbidity and mortality, suffering and associated clinical symptoms, chronic heart failure is comparable to cancer [1]. In oncological patients, the treatment of symptoms plays an important role, and not only in the terminal stages of the disease. If compared to palliative care provided to oncological patients, we can see a significant imbalance in the provision of palliative care to patients with chronic heart failure [6]. However, the importance of palliative care also in this area has become increasingly evident. Some of the findings are taken from experience with the treatment of oncological patients where symptomatic opioid-based treatment has its inalienable position [7].

Opioids and dyspnoea

Opioids include natural opioids contained in the resin produced by the opium poppy (morphine) and its derivatives – esters of morphine (heroin), semisynthetic opioids (hydromorphone and oxycodone) and fully synthetic opioids (fentanyl, methadone and tramadol). These are substances that bind to one or more of the three opioid receptors – mu, delta and kappa [8].

Opioids utilize several mechanisms to relieve dyspnoea – reduction in respiratory rate, reduction in tidal volume, reduction in the central perception of dyspnoea (reduction in the perception and reaction of the respiratory centre to hypoxaemia and hypercapnia), change in the activity of the peripheral opioid receptor in the airways (the highest density of the opioid receptor binding sites is located in the walls of alveoli, in the smooth muscles of the trachea and primary bronchi) and reduction in the degree of anxiety [9,10].

Alveolar ventilation is primarily an automatic process which is controlled by chemoreceptors. Breathing responds to signals transmitted from peripheral chemoreceptors to centres located in the medulla oblongata. These receptors are very sensitive to any increase in the partial pressure of carbon dioxide (pCO_2). They respond less sensitively to any decrease in the partial pressure of oxygen (O_2) and pH. A small increase in pCO_2 is enough to induce an increase in tidal volume to ensure normocapnia. Opiates can cause a decreased sensitivity of the respiratory centre to an increasing concentration of pCO_2. Respiratory depression, reduced ventilation associated with the increase in pCO_2 and the subsequent reduction in pO_2 are the most feared adverse effects associated with opiate treatment.

These aspects were investigated by Clemens in her research. However, she failed to prove an increased risk of respiratory depression in those patients who were treated with strong opioids compared to those patients who did not receive this treatment [11]. Also in the meta-analysis by Jennings no harmful effect of opioids on the values of blood gases and saturation by oxygen were proven [9]. Clinically significant respiratory depression is unusual with low doses, also namely in older patients [12].

Side effects of opioids, tolerance and addiction, withdrawal syndrome

Among the additional most common side and adverse effects of opioids are constipation, nausea, vomiting, aggravated emptying of the urinary bladder, dry mouth and sedation. Tolerance to the side effects such as nausea and vomiting develops relatively quickly in an opioid-naive patient, however, in the case of constipation such tolerance does not develop at all. All the adverse effects are to a greater extent curable and should not be the reason for the discontinuation of the opioid treatment. On the contrary, we should foresee the incidence of such adverse effects and take relevant precautions, such as the prescription of laxatives to attenuate constipation and antiemetics to attenuate nausea [9,10].

Another reason for limiting the use of opioids in medicine is the development of tolerance. It is characterized by a gradually decreasing response to treatment with the necessity to increase the dose needed for the attainment of the desired effect.

Among the worst adverse effects are the development of dependency and pathological psychological addiction – drug abuse. Dependency is an adaptation physiological phenomenon characterized by the development of withdrawal syndrome in the organism which occurs in relation to a considerable reduction in the dose of opioid or a sudden discontinuation of treatment. The symptoms of hyperactivity of the sympathoadrenal system such as anxiety, severe restlessness, irritability, pain threshold reduction, sweating, rhinorhea, lacrimation, piloerection, stomach cramps, diarrhoea, raised heart rate, raised blood pressure and insomnia, dominate. In the case of a sudden withdrawal of opioids,

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