ORIGINAL ARTICLE

EVIDENCE OF STRONG OPIOID THERAPY FOR PALLIATION OF BREATHLESSNESS IN CANCER PATIENTS

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Abstract

At the end of life, approximately one third of cancer patients experience moderate to severe breathlessness. A good control of this symptom requires non-pharmacological and pharmacological interventions, the latter being limited to bronchodilators, furosemide, steroids, and strong opioids. The role of oral, subcutaneous, or intravenous morphine has been proven to manage breathlessness since the 19th century. Highlighting the peripheral opioid receptors in the respiratory tract, the treatment with strong opioids has become the gold standard in the management of intractable breathlessness. The present research aimed to find new evidence regarding the use of strong opioids in the treatment of breathlessness, for the doses and type of opioids indicated, the concurrent drugs allowed and the influence on respiratory parameters. Questions regarding the establishment of the standard opioid dose and the efficiency of the nebulized, transmucosal or intranasal administration remained unanswered..

Rezumat

La finalul vieții, aproximativ o treime din pacienții cu cancer acuză dispnee de intensitate moderată până la severă. Tratamentul dispneei impune măsuri non-farmacologice și farmacologice, acestea din urmă fiind limitate la bronhodilatatoare, furosemid, corticoizi și opioide majore. Rolul morfinei, în administrarea orală, subcutanată sau intravenoasă, în tratamentul dispneei, a fost dovedit încă din secolul XIX. Odată cu evidențierea receptorilor opioizi periferici prezenți la nivelul tractului respirator, tratamentul cu opioide puternice a devenit standardul în managementul dispneei intractabile. Cercetarea prezentă urmărește evoluția tratamentului cu opioide majore, a dozelor și tipului de opioizi, cu indicație în controlul dispneei, asocieri terapeutice permise și influența asupra parametrilor respiratori. Rămân întrebări deschise în vederea standardizării dozelor și stabilirea eficienței administrării inhalatorii, transmucozale sau intranazale a opioidelor majore.

Keywords: opioids, breathlessness, cancer

Introduction

The American Thoracic Society consensus statement defines breathlessness as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from the interaction among multiple physiologic, psychological, social, and environmental factors, and may induce secondary physiologic and behavioural responses" [2].

In cancer, breathlessness occurs due to primary or metastatic invasion of the lungs, pleural effusions, underlying chronic obstructive pulmonary disease (COPD), infections, pulmonary embolism, or chronic heart failure. Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness) [25].

Thus, treatment should initially focus on the salient causes of breathlessness, such as correction of hypoxemia with supplemental oxygen, acute hypercapnia treatment with non-invasive positive-pressure ventilation, reversal of bronchospasm with agonist and steroids, relief of chest wall restriction by drainage of pleural effusions or ascites, and reduction of pulmonary oedema with diuretics. Refractory breathlessness represents the persistence

of the symptom after the optimal treatment of the underlying causes and represents a therapeutic challenge.

Opioids have been used to treat breathlessness since the late 19th century, but their use has declined in the 1950s, once a clear relationship has been established with respiratory distress. In the 1980s, the peripheral opioid receptors were discovered throughout the body, thus increasing the possibility of a targeted treatment for breathlessness with nebulized opioids, with fewer side effects [15].

Breath acts mainly to signals that are transmitted from the peripheral chemoreceptor to the respiratory centre from *medulla oblongata*. These receptors are highly sensitive to an increase in the partial pressure of arterial CO_2 (pCO_2) and the reaction is less sensitive to a fall in the arterial pH and arterial partial pressure of O_2 [17]. Opioids are able to reduce the breathing centre in response to the increase in pCO_2. The administration of opioids will increase the ventilation less when pCO_2 grows due to a higher tolerance to the increase of arterial CO_2 [17, 21].

Three main opioid receptors have been identified in the respiratory tract: μ(MOR), δ(DOR), and κ(KOR), which mediate the effects of the 3 primary families of endogenous opioids (endorphins, enkephalins, and dynorphins, respectively) as well as exogenous opioids such as morphine and codeine. In addition, the lungs may also contain a novel opioid receptor in the trachea, bronchi, and pulmonary arteries, but these receptors are particularly prominent in the bronchioles and the alveolar walls near the pulmonary capillaries and are associated with vagal afferent C-fibres [28]. Opioids may modify the signal of these fibres or stimulate the pulmonary stretch receptors and alter the perception of breathlessness. Also, initially, opioids could decrease the anxiety accompanying the sensation of shortness of breath [15, 26].

The anterior islet and other brain structures are commonly activated during the perception of breathlessness and pain. Many of these brain regions that process the perception of pain and breathlessness can be pharmacologically modulated by opioids and benzodiazepines [4, 10, 16].

The strong opioids-morphine, diamorphine, fentanyl, hydromorphone, represent the only group of drugs for which there is evidence in the symptomatic treatment of refractory breathlessness [15, 24]. Palliative therapy with opioids should be considered only when conventional approaches do not produce satisfactory results or corrective treatment is not plausible.

Materials and Methods

A systematic review of literature in English was conducted in search electronic databases. PubMed and MEDLINE were browsed by using search terms such as “breathlessness”, “opioid”, “cancer”, “neoplasm”, “morphine”, “fentanyl”, “oxycodone”, “hydromorphone”, from January 2000 until present. After scanning abstracts, clinical trials and revisions of literature were selected according to strong opioid treatment in cancer breathlessness in adult patients. Clinical trials with sustained results to which full-text access was granted, were identified, and revisions of literature were used to complete the records.

Results and Discussion

145 abstracts published since 2000 until now were identified, out of which 29 met the inclusion criteria: 11 articles - reviews of literature, 2 - therapeutic guides, 3 - letters to the editor, 1 - case presentation, 2 - retrospective studies, 4 – non - randomized prospective or observational studies, 2 - randomized sequential single - blind, 4 - randomized double - blind.

The efficiency of strong opioid therapy, in subcutaneous or systemic forms, in the control of cancer breathlessness, has been recognized since the 1980s. Recent studies have mainly focused on identifying the effectiveness of other forms of administration - nebulization, transmucosal (including intranasal administration), in combination with benzodiazepines, identifying the mechanism of action at the peripheral opioid receptors and at the central level and identifying the effect on respiratory constants.

It is known that the doses of sustained-release morphine (a narcotic pain reliever used for around-the-clock treatment of moderate or severe pain) have been shown to safely reduce breathlessness in cancer patients with chronic breathlessness. Patients should be initiated at a dosage of 10 mg/24 h and titrated by 10 mg if there is no initial benefit [10].

Opioids work significantly better than oxygen in reducing the intensity of breathlessness even in hypoxic patients [8]. Morphine is the most common of the opioids used to relieve breathlessness, and can be administered *via* oral, parental, and nebulized routes. Although the oral or IV route is currently the treatment of choice, many randomized, controlled studies have been performed to determine the efficacy of nebulized morphine.

Some studies have reported a rapid control of breathlessness in the treatment with nebulized opioids, but there is considerable variability regarding the type and doses of opioid recommended.

A review of literature by Kallet *et al.* concluded that in cancer patients who suffer from intractable breathlessness, relatively small amounts of inhaled opioids appear to improve the breathing comfort, despite the fact that these patients are already receiving high levels of parenteral opioids for pain management [15]. Charles *et al.* reported the results of

a comparative pilot study of systemic opioid *versus* nebulized opioid and nebulized saline. Results indicated that nebulized hydromorphone, systemic hydromorphone, and nebulized saline produce rapid and statistically significant improvements in breathlessness, only nebulized hydromorphone producing an improvement large enough to be considered clinically important [6].

A small prospective nonrandomized trial showed a significant decrease in the intensity of breathlessness at rest and on exertion and a significant decrease in the intensity of anxiety and no significant arterial pressure of CO_2 increase or oxygen saturation (SaO_2) decrease after the first opioid administration [7]. Since 1984, Walsh *et al.* has investigated 20 patients whose pain was relieved, the influence of opioid treatment on respiratory function being noticed. All the patients received > 100 mg/day oral morphine. The results of this study showed no decrease in the respiratory rate - and merely a small increase in the arterial $paCO_2$ [25]. A double-blind randomized controlled study of 11 patients with advanced cancer showed that both nebulized and SC morphine could decrease baseline breathlessness, the response was sustained for over several hours and that there was no difference in breathlessness relief between subcutaneous and nebulized morphine [5]. Morphine, fentanyl, hydromorphone, and oxycodone are some of the most common opioids used to manage breathlessness. Currently, there has been no evidence for the efficacy of fentanyl in episodic breathlessness, a decrease in the intensity of breathlessness after the administration of fentanyl being identified, but without statistically significant differences from placebo [24]. The most common form of fentanyl administration (nebulized or intranasal) has been studied [24]. Benitez Rosario *et al.* reported 4 case presentations that identified the efficiency of treatment with oral transmucosal fentanyl citrate, with rapid relief of breathlessness, without intolerable side effects and without changing respiratory distress and oxygen saturation [3]. Navigante *et al.* assessed the role of midazolam as an adjunct therapy for morphine in the alleviation of severe breathlessness perception during the last week of life, in patients with advanced cancer because, during the episode of severe breathlessness, patients experience respiratory panic attacks (severe anxiety), too [18]. The study showed that the beneficial effects of morphine in controlling the baseline levels of breathlessness might be improved with the addition of midazolam to the treatment. The number of episodes of breakthrough breathlessness when patients received both drugs from the beginning was lower than that in the other two groups (around-the-clock morphine and rescues with midazolam or around-the clock midazolam and rescues with morphine). During the first 24 hours, breathlessness was better controlled in those patients receiving the combination of drugs on an around-the-clock basis. This group also had fewer patients (only 4%) with uncontrolled breathlessness at 48 hours. Thus, midazolam was more likely to increase the efficacy of morphine in controlling breathlessness when both drugs were administered together [18]. Also, morphine and midazolam have proven effective on long-term administration and midazolam was more effective in controlling the continuing and breakthrough components of breathlessness during the ambulatory follow-up [19]. A more recent uncontrolled trial of inpatients with cancer without comorbidities found that the combination of lorazepam and opioids relieved breathlessness and did not cause respiratory depression [9]. Moreover, Gomutbutra *et al.* found that patients who received both benzodiazepine and opioids were significantly more likely to report an improvement in breathlessness than those treated with opioids alone or with no medications, but supported the use of opioid treatment at baseline [12].

A randomized continuous sequential clinical trial assessing the response in breathlessness from breakthrough doses of morphine in 35 participants with terminal cancer found that those with lower baseline breathlessness intensity had a three times higher response to morphine than those with more severe breathlessness, although this was not statistically significant ($p = 0.1$) [1, 14]. Patients with worse breathlessness intensity were more likely to gain a net benefit from opioid treatment and older people were at a particular risk of drug - drug and drug - host - related adverse events [14].

Table I

Summary of studies

Author, Year	Design	N	Intervention	Evaluation	Results
Benitez-Rosario *et al.*, 2005 [3]	Case Presentation	4	Fentanyl transmucosal rescue dose	Subject report, SaO_2	Breathlessness was improving rapidly without decreasing SaO_2
Bruera *et al.*, 2005 [5]	Randomized, crossover, double-blind	12	Nebulized morphine 50% of around-the-clock regular dose Subcutaneous morphine 50% of around-the-clock regular dose	VAS at baseline and at every 15 minutes for the first 1.5 hours	Non statistically significant difference ↓ breathlessness at 60 min

Author, Year	Design	N	Intervention	Evaluation	Results
Navigante *et al.*, 2006 [18]	Randomized, single-blind	101	Mo - around-the-clock morphine sc (2.5 mg + 25% daily dose) + midazolam sc 5 mg rescue dose Mi - around-the-clock midazolam sc (5 mg) + morphine 2.5 mg, sc, rescue dose MM - around-the-clock morphine sc (2.5 mg + 25% daily dose) + midazolam 5 mg + Morphine rescue dose, sc, (2.5 mg)	Borg Scale at rest (baseline, 24 h and 48 h after intervention)	Morphine + midazolam was more effective than morphine or midazolam alone
Charles *et al.*, 2007 [6]	Randomized controlled double-blind crossover	20	5 mg nebulized hydromorphone Systemic dose of hydromorphone 3 mL or nebulized saline with a blinding agent Breakthrough dose	Subject report	Rapid improvement clinically important for nebulized hydromorphone ↓ significantly for all treatments over time
Clemens *et al.*, 2007 [7]	Prospective non - randomized	11	Opioid at every 4 hours + 1/6 daily dose for breakthrough breathlessness	Partial CO_2 tension Oxygen Saturation, Pulse frequency	Opioids significantly improve the intensity of breathlessness No significant changes in other monitored respiratory parameters
Clemens *et al.*, 2009 [8]	Prospective non - randomized	46	25% increase in the opioid dose Dose titration in opioid naive patients	Respiratory parameters at baseline and at every 30 minutes until 2 h to intervention	↑ significantly SaO_2 on hypoxic patients ↓ significantly respiratory frequency in all groups of patients
Goodridge *et al.*, 2010 [13]	Retrospective	602 433	Opioid prescription for lung cancer *vs.* COPD in the last 3 months of life	Administrative data Opioid dispensing	Opioid are dispensed for a small proportion of patients with COPD
Navigante *et al.*, 2010 [19]	Randomized, sequential, single-blind	63	Morphine (oral)/4 h, starting dose: 3 mg Midazolam (oral)/4 h, starting dose: 2 mg	Numerical rating scale (NRS) - follow-up phase Breathlessness relief five-category scale - fast titration phase	↓ intensity in NRS in both groups on day 2, Midazolam group was superior on days 3, 4, 5
Gamborg *et al.*, 2013 [11]	Randomized double-blind, double-dummy	20	Red morphine drops Subcutaneous morphine	VAS during 60 minutes after intervention	Statistically significant effect for both treatments
Gomutbutra *et al.*, 2013 [12]	Retrospective	115 73	Opioids alone Benzodiazepines concurrent with opioids Benzodiazepines alone	Subject report	Improvement in breathlessness after 24h to intervention Benzodiazepines concurrent with opioid were independently associated with an improvement in breathlessness
Pang *et al.*, 2014 [20]	Prospective observational	16	Intravenous fentanyl	Subject report	Not statistically significant
Pinna *et al.*, 2015 [22]	randomized double-blind, crossover	13	Transmucosal fentanyl *Placebo*	ESAS, oxygen saturation, distance walked	Not statistically significant
Schmitz *et al.*, 2015 [23]	Observational	18	Systemic opioid	Self-reported numeric rating scale Richmond Agitation Sedation Scale Scores	Systemic opioid is feasible, Daily morphine equivalent dose - day 1 - 20.3 mg Daily morphine equivalent dose - day 2 - 13.0 mg Daily morphine equivalent dose - day 3 - 16.0 mg

Conclusions

Therefore, the mainstay of breathlessness palliation remains morphine, as the first choice in pharmacological therapy, acting by altering the central perception. Systemic opioids orally or parenterally administered can be safety used to manage breathlessness in cancer patients, without increasing the risk of respiratory distress.

For patients with intractable breathlessness under treatment with sustained-release morphine, the combination of nebulized opioids (rescues doses) or benzodiazepines (around the clock doses) can improve the breathing comfort.

Questions regarding the optimum starting dose, regimen, opioid choice, choice of modified or normal-release formulation, and the indications for parenteral use, remain unanswered.

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