Chapter

Other Uses of Morphine

Shrenik Ostwal

Abstract

Worldwide many different strong opioids and their formulations are available to control pain. Of which, morphine is considered as global opioid of choice and is widely used to control moderate to severe pain. The World Health Organization (WHO) has recommended morphine as one of the essential drug. Apart from analgesic use, research has proven its effectiveness for relief and treatment of various debilitating and distressing conditions like breathlessness, mucositis (oral and vaginal) and cough. However, its role in diarrhea and opioid substitution therapy (OST) is still nonconfirmatory. This chapter illustrates all available literature supporting effectiveness of morphine in above conditions and its impact on quality of life.

Keywords: morphine, dyspnoea, mucositis, chronic cough, opioid substitution therapy (OST), diarrhea

1. Introduction

Preparations of the opium poppy *Papaver somniferum* have been used for many hundreds of years to relieve pain. Morphine remains as the gold standard for management of moderate to severe cancer pain. It has a five ringed structure with a characteristic T-shaped three dimensional form essential for activation of the opioid receptor.

Due to its strong affinity to mu receptors and action similar to endorphins, i.e., natural pain killers, morphine has been widely used globally. Apart from its analgesic action, it can be used widely for symptomatic relief of other distressing and debilitating conditions. This chapter depicts all available literature for various other uses of morphine.

2. Dyspnoea

2.1 Introduction

Dyspnoea, also termed as breathlessness, is a common and prevalent source of discomfort in patients with advanced cancer and non-cancer life limiting illnesses. Most people describe it as an uncomfortable sensation or increased work of breathing in terms of air hunger, increased effort, chest tightness, rapid breathing, incomplete exhalation or feeling of suffocation.

The American Thoracic Society defined dyspnoea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. This definition highlights key areas where dyspnoea can be measured, suggesting that dyspnoea is not merely a single sensation but a shared experience with physical and affective components. This is similar to concept of

total pain or total suffering which constitutes other domains like psychological, social, spiritual and environmental.

The prevalence of dyspnoea varies according to disease primary site and stage of illness. Studies by Muers and Round [2]; Smith et al. [3] reported prevalence of dyspnoea in 75–87% patients with primary lung cancer. While, a systematic review by Solano et al. [4] reported dyspnoea prevalence of: 90–95% in patients with chronic obstructive pulmonary disease (COPD), 60–88% in patients with heart disease, 11–62% in patients with AIDS and 11–62% in patients with renal disease. COPD and chronic heart failure (CHF) constitutes major non-cancer causes of dyspnoea in patients [5, 6].

Dyspnoea due to its prevalence and associated suffering poses a significant burden to patients and caregivers, hence severely affecting quality of life.

2.2 Pathophysiology of dyspnoea

Normally during unconscious activity, respiration is managed by clusters of neurons in the medulla. They receive afferent input from several types of mechanoreceptors in respiratory muscles, airways, and lung parenchyma and chemoreceptors in aortic and carotid bodies and the medulla. Motor commands from the medulla or motor cortex by means of the medulla descend to respiratory muscles through efferent motor neurons [7, 8].

Differential diagnosis for dyspnoea in advanced cancer can be: (**Table 1**).

2.3 Opioids in breathlessness

The primary site of action of opioids in breathlessness is through medulla oblongata, although various mechanisms may be involved on effect on perception of breathlessness. **Box 1** suggests various mechanisms by which morphine acts on breathlessness [1].

- Analgesia—reduction of pain induced respiratory drive.
- Anxiolytic effects.
- Reduce minute ventilation.
- Cortical sedation (suppression of respiratory awareness).
- Alteration of neurotransmission within medullary respiratory center.
- Reduce central sensitivity and response to hypercarbia or hypoxia.
- Decreased metabolic rate and ventilatory requirements—decrease in O_2 consumption.
- Vasodilatation and improved cardiac functions.

Box 1.
Mechanism by which morphine reduces perception of breathlessness. Source: Adapted from American Thoracic Society guidelines on dyspnoea 2012.

A study by Mahler et al. [9] in 2009 demonstrated threefold increase in beta endorphin levels in 17 COPD patients when compared from rest to end exercise. Patients were randomized to receive either normal saline or 10 mg of intravenous naloxone. Authors found significantly higher peak ratings and regression slope of breathlessness with naloxone as compared to normal saline. This study high-lighten role of endogenous opioids in dyspnoea modification in COPD patients.

Research has demonstrated role of oral morphine in breathlessness. However dosing schedule varies according to underlying condition. **Box 2** depicts morphine dosing recommendations for breathlessness [10]:

- Opioids should be started when disabling dyspnoea persists despite maximal Management of underlying condition.
- Check for renal, hepatic, pulmonary function, current and past opioid use.
- Prescribe laxatives and other supportive medications.
- Adopt policy of "Start Low and Go Slow" while titrating morphine dosage.
- Titrate morphine dose (up to 25–50% of dose for continued mild to moderate dyspnoea; and by up to 50–100% of dose for continued moderate to severe dyspnoea) every weekly over 4 weeks until lowest effective dose is found.
- Start with 2.5–5 mg/4 h. PO or 1–2.5 mg/4 h. SC of morphine in opioid naive patients.
- For patients already prescribed morphine for pain, increase regular dose by 25–30%.
- Consider long acting twice daily morphine dosing in patients with stable regular dose.
- Consider 1/6th of regular dose prn for episodic breathlessness.

Box 2.
Morphine dosing recommendations for breathlessness. Source: Adapted and developed from best practice for managing breathlessness in palliative care.

Malignant causes	Non-malignant causes
Lung cancer/metastases to lung	COPD/interstitial lung disease
Pleural effusion/pericardial effusion/ascites	Bronchiectasis
Superior vena caval obstruction	Congestive heart failure
Pulmonary embolism	Arrhythmias
Pulmonary edema	Motor neuron diseases
Major airway obstruction	Muscular dystrophy
Lymphangitis carcinomatosis	Anaemia
Chest wall infiltration	Acidosis
Radiation induced pulmonary fibrosis	Anxiety/panic attacks

Table 1.
Causes of dyspnoea.

2.3.1 Morphine for breathlessness in cancer patients

There is good evidence for role of opioids in breathlessness [1, 5, 11–20]. Most of studies illustrated beneficial effect of morphine in breathlessness in cancer patients. Out of eight studies which evaluated effect of morphine in cancer related dyspnoea, seven were randomized controlled, double blind trials [21]. Another study by Clemens et al. [22], a non-randomized prospective study in advanced terminal cancer patients with dyspnoea, reported beneficial effect of morphine in reducing intensity of dyspnoea when compared with oxygen. While, Charles et al. [23] also reported similar and rapid improvement in breathlessness with use of nebulised hydromorphone. Studies by Bruera et al. [15] and Mazocato et al. [24] compared role of subcutaneous morphine with placebo in patients with primary lung cancer or lung metastases, showing a significant decrease in breathlessness intensity on visual analogue scale (VAS) after 45 min of intervention when treated with morphine. This was supported by a meta-analysis by Ben-Aharon et al. [10] in patients with cancer related dyspnoea. Authors found positive effect of opioids in reducing breathlessness.

Another two studies by Davis et al. (1996) and Grimbert et al. [25] reported no significant improvement in VAS scores even after 60 min of intervention with nebulized morphine when compared with placebo, i.e., nebulised saline. In one study Bruera et al. [15] compared effect of subcutaneous morphine with nebulised

morphine in lung primary patients, reporting no significant difference in dyspnoea intensity. However, this study reported patient's preference with nebulised morphine. Lastly, Allard et al. [26] found no significant differences in VAS score with 25 or 50% increments in morphine dosages.

2.3.2 Morphine for breathlessness in COPD patients

A systemic review and meta-analysis by Jennings et al., comparing opioids with placebo for the treatment of dyspnoea [21] showed out of 18 randomized controlled trials (RCT) involved, nine trials reported patients receiving either oral opioids (n = 8) or subcutaneous morphine (n = 1). Such patients experienced significant beneficial effect with parenteral opioids on reducing dyspnoea when compared with placebo (meanΔ: −0.40; CI: −0.32 to −0.17). However, exercise was used as provoking stimulus to dyspnoea in eight of these nine studies, whereas only one study could examine patients with dyspnoea at rest.

Another randomized, double blind, placebo-controlled crossover trial by Abernethy et al. [27] compared 4 days of 20 mg oral sustained-release morphine with 4 days of oral placebo. Thirty-eight (87.5%) participants who were opioid naive and had dyspnoea at rest in spite of optimal therapy for their underlying condition (mainly patients with COPD) completed the trial. Patients on morphine experienced significant improvements (i.e., less dyspnoea and improved sleep) on VAS scale. Hence, authors concluded that "sustained release, oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnoea in the community setting."

2.3.3 Morphine for breathlessness in heart failure patients

Only few published studies have demonstrated positive outcomes with use of morphine in CHF related dyspnoea. In a pilot study by Johnson et al. [28] aimed to measure effect of oral morphine on breathlessness in patients with CHF, authors found a significant decrease in median breathlessness in those who received 5 mg of oral morphine four times a day (p = 0.022), whereas no change was observed in patients treated with placebo.

Oxberry et al. [29] conducted a crossover RCT on 35 patients diagnosed with CHF (New York Heart Association Grade III–IV) comparing 4 days of morphine (5 mg four times daily), oxycodone (2.5 mg four times daily) and placebo followed by a washout period of 3 days. Patients were followed up for 3 months. Authors found a significant improvement in composite breathlessness in opioid group as compared to placebo (p = 0.017). However they did not find any statistically significant difference in breathlessness improvement in either intervention group. Hence, authors concluded need for long term trials to establish effectiveness of opioids.

Before stating opioids for dyspnoea in CHF patients, all possible etio-pathological causes should be taken into consideration. Non-pharmacological treatment options—salt and fluid restriction, diet modification, appropriate exercise training and weight reduction strategies, etc., should be used first. Pharmacological therapy with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, diuretics, digoxin and implant devices should be optimally considered. Other possible causes like anaemia and pleural effusion should be taken care of.

2.3.4 Morphine for breathlessness in other conditions

A recent double blind study by Shohrati et al. [30] on 40 patients presented with dyspnoea due to mustard gas induced bronchiolitis obliterans reported

effectiveness of nebulised morphine (1 mg diluted in 4 cc normal saline). Patients experienced improvements in dyspnoea VAS score, cough, night time awakenings both due to dyspnoea and cough, heart rate, respiratory rate and overall quality of life.

A phase I clinical trial on six patients with interstitial lung disease (ILD) by Matsuda et al. [31] comparing two different doses of subcutaneous morphine injection demonstrated a tolerable dose of 2 mg to alleviate dyspnoea. However due to small sample size, results could not be reciprocated to general population and need for larger trials were recommended. On the other hand, Harris-Eze et al. [32] does not found any significant difference in exercise capacity and dyspnoea score in ILD patients treated with either 2.5 or 5 mg of nebulised morphine. This was supported by Cochrane review by Polosa et al. [33].

A single arm study of six patients with terminal amyotrophic lateral sclerosis (ALS) by Clemens et al. [22] showed effectiveness of morphine in reducing dyspnoea. Authors found a significant difference in respiratory rate and dyspnoea intensity at 120 min after morphine administration.

3. Role of morphine in mucositis

Mucositis refers to erythematous, erosive and ulcerative lesion of mucosa observed in patients with cancer treated with chemotherapy and/or radiotherapy to fields involving areas of body. Accordingly it may involve oral cavity, gastrointestinal tract, vaginal mucosa or other areas. Hence, manifesting as burning pain in mouth, diarrhea, vaginitis, etc. Elting et al. [34] observed chemotherapy-induced mucositis in 303 out of 599 patients (51%). Oral mucositis was developed in 22% cycles while gastrointestinal (GI) mucositis in 7% cycles.

3.1 Pathophysiology of mucositis

The five-stage model depicts various steps involved in pathogenesis of mucositis. Stages involved are [35]:

1. Stage of initiation of tissue injury
2. Stage of signaling through up regulation of inflammation *via* generation of messenger signals
3. Stage of amplification
4. Stage of ulceration and inflammation
5. Stage of healing

3.2 Morphine and oral mucositis

Oral mucositis poses a significant source of pain and distress to patients receiving chemotherapy or radiotherapy to head and neck area. It often manifests as burning pain, ulcers, erythematous lesions in mouth complicated by secondary infections—bacterial/fungal/viral. It significantly affects nutritional intake, oral hygiene and overall quality of life. Infections associated with oral mucositis may pose life-threatening conditions. Adequate oral hygiene and treatment of underlying cause helps to relieve symptoms and distress in patients [36, 37].

Various combination of local measures helps to take care of mucositis-related complications. Research has shown effectiveness of morphine gargles either alone (morphine rinse) or in combination with antacid, lignocaine viscous and dextromethorphan (magic mouth wash), in relieving pain and symptoms related to mucositis. A mini review by Dutta et al. [38] compared six studies using morphine as oral rinse. All studies showed satisfactory result in terms of pain control, mouth opening and patient preferences. This is supported by other studies which proved efficacy of morphine gargles [36, 37, 39–44].

3.3 Morphine and vaginal mucositis

Vaginitis, also known as vaginal mucositis is an acute inflammation with erythema and erosion of vaginal mucosa leading to severe vaginal pain, per vaginal discharge and/or associated complications. It is commonly seen in patients with local infection or as a part of systemic infection, as a complication to radiotherapy to local areas or chemotherapy, recto-vaginal fistula, trauma, etc. Morphine, similar to its role in oral mucositis can be considered for vaginal mucositis. A case reported by Ostwal et al. [45] showed efficacy of morphine when combined with vaginal douche (magic vaginal douche—metronidazole, normal saline, povidone iodine solution, lignocaine viscous with 20 mg crushed tab morphine) in relief from symptoms of vaginal mucositis. However RCTs are not available and are required to prove its clinical efficacy.

4. Role of morphine in chronic cough

4.1 Introduction

Cough is found to be prevalent in around 65% patients with lung cancer [46] and 70% patients with COPD [47, 48]. Persistent or chronic cough can have various physical complications like musculoskeletal pain over chest wall, rib fracture, bowel and bladder incontinence, disturbed sleep and feeling of exhaustion. Patients usually experience psychological impacts, social isolation and decreased quality of life [48].

Cough reflex is regulated by vagal afferent pathways, nucleus tractus solitarius (NTS) in brainstem, and cough center in cerebral cortex. Common underlying patho-physiological causes for cough includes: (i) infection; (ii) lung cancer or secondary metastases to lung/pleura/mediastinum/pericardium/blood vessels; (iii) COPD, ILD, bronchiectasis; (iv) aspiration; (v) asthma/bronchospasm; (vi) esophageal reflux; (vii) tracheo-esophageal fistula; (viii) radiotherapy or chemotherapy induced pulmonary fibrosis; (ix) ACE inhibitors; (x) pulmonary edema/left ventricular failure, etc. Timely and proper assessment of cough with removal of underlying cause can decrease distress and improve patients' quality of life.

4.2 Morphine and cough

Research work by Kamei [49] showed involvement of mu opioid receptors in production of cough. Very limited studies are available for use of morphine on chronic cough [47, 50–56]. Strongest evidence for effectiveness of morphine in chronic cough was shown in a double blind placebo controlled trial by Morice et al. [57]. Twenty seven patients with chronic persistent cough were assigned to 4 weeks of slow release morphine sulfate (5 mg twice daily escalated to 10 mg twice daily) matched correspondingly with placebo. A significant improvement of 3.2 points

over baseline, and 40% rapid reduction in cough frequency and severity was observed in slow release morphine group ($p < 0.01$). Dose comparison over 3 month period between 5 and 10 mg did not showed any significant difference, helping to conclude study with daily dose recommendation of slow release morphine sulfate from 5 to 10 mg twice daily.

5. Role of morphine in diarrhea

Diarrhea has been defined as "passage of ≥3 loose or watery bowel movements per day or passage of ≥200 g of stool per day based on typical diet." Diarrhea can be acute (<14 days), persistent (>14 days but <30 days) or chronic (>30 days) based on its duration. Diarrhea poses a common and significant problem in patients with cancer. It may be due to either local infection, as a part of systemic inflammation/infection, as a complication to radiotherapy or chemotherapy [58], etc.

Mechanism for diarrhea can be attributed to increased intestinal motility [59, 60]. Hence drugs which act to decrease intestinal motility are found to be helpful in treatment. Morphine and other opiates (loperamide, diphenoxylate, codeine) act on intestinal mu-receptors and slow intestinal transit time, thus increasing net absorption [61, 62]. Though constipation is commonly seen as a side effect with morphine use, research considering use of this side effect to treat diarrhea has not been done. Clinical Practice guidelines by European Society for Medical Oncology (ESMO) has documented role of tincture of opium like morphine (10 mg/mL morphine) in treatment with diarrhea as an alternative to loperamide. The recommended dose of tincture morphine is 10–15 drops in water every 3–4 h [58, 63, 64]. Till date robust studies supporting this has not been available.

6. Morphine and opioid substitution therapy (OST)

Morphine has been known for its potential effect in analgesia since last few decades. However, it is also known for its potential to cause addiction and dependence. Opium, derived naturally from poppy plant is widely used for addiction. Opioid substitution therapy (OST) is an evidence-based intervention for opiate dependent persons that replaces illicit drug use with medically prescribed, orally administered opiates such as buprenorphine and methadone. OST reduces HIV risk behaviors and harms associated with injecting (such as abscesses, septicemia and endocarditis), overdose and participation in criminal activity, thereby improving the quality of life and health of injecting drug users (IDUs).

Work by Hämmig et al. [65] showed that slow release oral morphine (SROM) preparations can be used as OST for heroin addicted patients. Authors found higher treatment satisfaction, fewer cravings for drug and less mental stress with SROM. Cochrane review by Ferri et al. [65] found only three randomized controlled trials which included SROM for OST. Out of three, only two studies suggested possible role of SROM formulations; while remaining study was associated with adverse events like depressive symptoms [65–70]. Hence authors concluded for necessity of more robust and clinically controlled trials.

7. Conclusion

Morphine, a potent and strong opioid, has shown its efficacy in relieving variety of distressing symptoms. Research has documented role of low dose morphine for

treatment and relief from conditions like chronic, refractory breathlessness, cough, mucositis (oral/vaginal). However, more robust studies are required to establish its clinical efficacy in diarrhea and opioid substitution therapy.

Conflicts of interest

None.

Author details

Shrenik Ostwal
Narayana Super Speciality Hospital, Howrah, West Bengal, India

*Address all correspondence to: drshrenikostwal@gmail.com

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