Respiratory depression secondary to morphine use in a patient with COPD and refractory breathlessness

To the Editor:

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction and progressive respiratory failure. Patients develop increasing breathlessness, which can persist despite optimal medical management (refractory chronic breathlessness) [1]. Various studies suggests that low-dose morphine may safely reduce refractory breathlessness in patients with advanced respiratory disease [2–6]; however, the recent population cohort study by Vozoris *et al.* [7] in the *European Respiratory Journal* suggests opioids may be associated with increased adverse respiratory outcomes, including death in older COPD patients. We report a case of respiratory depression secondary to opioid use for refractory breathlessness.

A 69-year-old man with severe COPD (forced expiratory volume in 1 s 0.8 L (25% predicted), forced vital capacity 3.2 L (75% predicted) and diffusing capacity of the lung for carbon monoxide 9 $mL \cdot min^{-1} \cdot mmHg^{-1}$ (30% predicted)) was admitted to our hospital with an infective exacerbation. Prior to admission, he had been an infrequent exacerbator and was known to have had severe, exertional breathlessness for a few years (Modified Medical Research Council Breathlessness Score of 3 out of 4). He had a very limited exercise capacity (6-min walk test distance 90 m with desaturation from S_{pO_2} 92% to 87% at 3 min), requiring ambulatory oxygen therapy. His usual COPD management included tiotropium (18 µg daily), budesonide/formoterol (200/6 µg, two puffs twice daily) and salbutamol (as required). He was not receiving domiciliary noninvasive positive pressure ventilation (NIV). He had previously completed a pulmonary rehabilitation programme but was not engaged in an exercise programme immediately before the admission. He also had multiple medical comorbidities, including ischaemic heart disease, hypertension, dyslipidaemia and anxiety.

The patient presented to hospital with increasing dyspnoea, fever and productive cough, and was found to have an elevated white cell count (23.2×10^9 per L) and C-reactive protein (58 $mg \cdot L^{-1}$). Renal function on admission was normal and remained stable during the admission. A chest radiograph did not demonstrate any focal consolidation. The patient was treated with hydrocortisone, benzylpenicillin, doxycycline, supplemental oxygen and regular nebulised salbutamol; however, NIV (arterial blood gas carbon dioxide tension 37 mmHg) was not required.

Despite optimal treatment for the exacerbation, on day 4, the patient had severe, distressing breathlessness at rest. He was therefore referred to a specialist palliative care department, which recommended regular, long-acting, oral morphine (10 mg *mane* and 5 mg *nocte*) with immediate-release morphine (2–3 mL of 1-$mg \cdot mL^{-1}$ solution) as required every 4–6 h for breakthrough breathlessness. Only 5 mg immediate-release morphine in total were required over the remaining 4 days of the admission. His dyspnoea was subsequently better controlled, with no signs of respiratory depression.

After 8 days in hospital, the patient was discharged home, where he lived alone, using the same morphine regimen for breathlessness. Laxatives were prescribed to prevent constipation. Verbal and written education regarding his medications was provided by a pharmacist prior to discharge. Follow-up in the respiratory clinic was arranged for 6 weeks later and he was advised to see his general practitioner (GP) in the interim.

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9 days later, the patient visited his GP, who found him drowsy and confused with respiratory depression. The GP administered naloxone and the patient was transferred to the hospital. In the emergency department, the patient had ongoing drowsiness and respiratory depression, requiring further naloxone. It became apparent that the patient had confused the laxative liquid and immediate-release morphine, and therefore had inadvertently consumed 30 mg morphine solution in addition to 10 mg extended-release morphine prior to visiting his GP.

The patient was monitored in a high-dependency unit, where he remained clinically stable and was discharged the following day. Despite further medication education, he could not safely self-administer immediate-release morphine; therefore, this was discontinued. Long-acting morphine twice daily was continued on discharge for his breathlessness.

This case highlights many important issues. The patient described had chronic severe breathlessness, which of itself may have been amenable to opioid treatment. However, opioid treatment was first indicated in the context of worsening breathlessness during an infective exacerbation. It is well recognised that the best treatment for breathlessness is to treat any underlying, reversible causes, such as infection. Thus, it is likely that with treatment for the patient's infection and with time, his breathlessness would have improved to baseline. Consequently, whilst morphine may have been appropriate during his admission, his longer-term morphine requirement and dosage were unknown.

Many international COPD guidelines recommend opioids to palliate distressing breathlessness in patients with advanced disease [8, 9]; however, currently, no guidelines suggest initiating opioids during an exacerbation. In COPD frequent exacerbators, 14–18% of first opioid prescriptions occur in the context of a respiratory exacerbation [10], despite a recent exacerbation being an exclusion criteria in opioid clinical trials.

In this case, respiratory depression occurred due to a significant patient dosing administration error, with the patient inadvertently consuming 10 times his prescribed, as-needed, immediate-release morphine dose. Dosing errors are well-recognised serious, adverse events; however, many COPD patients are older, live alone, have significant comorbidity and use multiple medications, any of which may increase the risk of serious toxicity or dosing error. Comorbidities, such as dementia and glaucoma, that can lead to patent dosing administration error occur more frequently in patients with COPD [11, 12], and individuals with cognitive comorbidities have been excluded from opioids breathlessness clinical trials [2, 3].

The US Food and Drug Administration recently announced new safety labelling changes for immediate-release opioids prescribed for pain, warning about the serious risks including addiction, overdose and death [13]. Off-license prescription of opioids for breathlessness requires even greater vigilance regarding serious events. Options for initiating morphine for refractory breathlessness include long-acting morphine (10 mg daily with up-titration weekly) [3] or immediate-release morphine (0.5 mg twice daily with up-titration weekly) [14]. However, the regimen for both immediate-release and long-acting morphine, which was used in this case and which is commonly used for pain, has not been studied in breathlessness trials. As the optimal morphine regimen for breathlessness is unknown, long-term morphine prescription requires careful consideration of risks and benefits, and dosing should be individualised using the lowest dose possible with up and down-titration according to response and side effects [15].

Similarly, when morphine is prescribed off-license, comprehensive medication education and ongoing, effective communication with the patient, family and other health professionals are essential. Initiating treatment as a stable outpatient, with close supervision and early review within 1–2 weeks (and not after 6 weeks as occurred in this case), allow these issues to be addressed, without the time pressures and often multiple medication changes, which may occur as an inpatient.

While morphine has a role in palliating refractory breathlessness, the additional complexity and challenges of off-label morphine prescription to respiratory patients reinforce the urgent need for further research in this clinical setting. In the interim, when considering morphine for patients with advanced respiratory disease and refractory breathlessness, we should remember, "first, do no harm".

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