Morphine for the symptomatic reduction of chronic breathlessness: the case for controlled release

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Abstract

Purpose of Review:

Clinicians who seek to reduce the symptomatic burden of chronic breathlessness by initiating regular low dose morphine have the choice of immediate or sustained release formulations - which will be better for this often frail population, and which has the more robust evidence to inform its prescription? Both formulations can be used.

Recent findings:

For chronic breathlessness, three factors consistently favour the use of regular, low dose, sustained release morphine over immediate release formulations:

1. Pharmacokinetics *in steady state* demonstrate lower peak and higher trough concentrations than immediate release formulations. From first principles, this profile is more likely to minimise harms and maximise benefits.

2. Meta-analyses studying patients who were treated *to steady state* in randomised, placebo-controlled studies for the indication of chronic breathlessness are almost all done with sustained and not immediate release formulations.

3. Studies consistently show patients' preferences for the least frequent dosing, with concomitant increases of up to 50% in otherwise poor medication compliance.

Summary:

As the evidence base expands for the symptomatic reduction of chronic breathlessness, pharmacological interventions will play a part. Using the best available evidence underpins patient-centred approaches that seek to predictably maximise the net effect.

As such, the weight of evidence in patient-centred clinical care favours the use of regular, low-dose sustained release morphine for the symptomatic reduction of chronic breathlessness.

Key words: breathlessness, morphine, medication compliance, net clinical effect, pharmacokinetics

Introduction

Is it better to use regular, low dose controlled release morphine or regular, low dose immediate release morphine for the symptomatic reduction of chronic breathlessness? Both can be used, and both have an evidence base. If the choice is available, which has the better evidence to underpin its prescribing in the frail population of people with chronic breathlessness?

This paper considers prescribing regular oral morphine for the symptomatic reduction of chronic breathlessness. Considerations of other opioids await further research. [1,2] Likewise, this paper does not consider other routes of morphine delivery such as parenteral, nebulised or rectal administration. The use of 'as needed' morphine for the symptomatic reduction of breathlessness is also beyond the scope of the request given to the authors for this article. The basis of the paper is the highest level of evidence to inform directly clinical practice in reducing chronic breathlessness, although that may not be the same as the clinical practice in many places.

Levels of evidence

The Centre of Evidence-Based Medicine at the University of Oxford has *pro forma* evaluation of the levels of evidence that is used to inform this current paper. [3]

Pharmacokinetics and pharmacodynamics of oral morphine formulations

From first principles, the aim of any therapy is to create a net clinical benefit. To do this, the benefits need to be maximised and the harms minimised. As clinicians in supportive or palliative care, we may tend to recall the benefits of therapies that we have prescribed and downplay any potential harms that the therapies we have prescribed may have caused. [4] In order to achieve a net benefit, the pharmacokinetic profiles of any available formulations of a medication need to be considered.

Morphine, unlike so many other medications, has a number of formulations, routes of administration and a wide range of doses available in order to deliver its clinical effects. For the oral route, formulations include immediate release morphine solution or tablets and modified (either controlled or sustained) release capsules or tablets. Each of these formulations have reproducible pharmacokinetic profiles in steady state that can help to inform clinicians' decisions about prescribing morphine for the symptomatic reduction of chronic breathlessness. [5]

Minimising toxicities for a receptor-modulated therapy such as opioids requires minimising the pharmacokinetic peak and having the highest troughs available. In work done *in steady state*, there are three distinct profiles (immediate release oral solution, controlled release and sustained release) each with differing highest and lowest concentrations. [5,6] Extrapolating from studies of anti-hypertensive medications, the trough to peak ratio is the parameter that describes the consistency and duration of a medication's effectiveness across the duration of its dosing interval. [7] Sustained release morphine in steady state has the lowest peaks and the highest troughs. [6]

Currently available evidence - effectiveness

The highest quality evidence on treatment effects comes from meta-analyses of randomized trials. A meta-analysis by Ekström *et al* considered systemic opioids for the symptomatic reduction of chronic breathlessness in patients with severe chronic obstructive pulmonary disease. [8] Of the three of eight studies that used morphine, 64 of 71 participants had sustained release morphine as the trial medication. All three of these studies were crossover trials. Only the first two of these studies, Abernethy *et al* (n=48) and Poole *et al* (n=16) (a) had placebo arms and (b) treated to steady state. [6,9] Of these two studies, only the study by Abernethy *et al* was rated as having a low risk of bias in all six parameters evaluated in the

meta-analysis and used formal measurement tools for both effectiveness and harms. The third study (n=7) was a single dose study comparing the effects of morphine and promethazine or prochlorperazine on exercise. [10] Like pain, single dose studies for chronic symptoms such as breathlessness should not be the basis of clinical decision making especially given the evidence of pharmacodynamic effects in chronic breathlessness several days beyond steady state pharmacokinetics. [11] The other five studies considered diamorphine (two studies; (n=24)) or dihydrocodeine (three studies; (n=47)). Studies of sustained release morphine in this meta-analysis were therefore the only studies that evaluated participants in steady state.

A second meta-analysis by Ekström *et al* also explored people treated with systemic opioids for breathlessness in people with advance disease. [12] Two additional studies were by Bruera et al (n=9) and Mazzocato et al (n=10) where people already on opioids for cancer pain were enrolled in a single dose, randomised, placebo controlled cross over study of an additional absolute dose of subcutaneous morphine. [13,14] Other additional studies included nebulised morphine, prophylactic fentanyl before exercise and a study of dihydrocodeine. [15-17] The overall findings again favoured systemic opioids over placebo for a clinically and statistically significant reduction in chronic breathlessness caused by a number of underlying aetiologies. [18] Where morphine was studied, the majority of participants were on a sustained release formulation.

One subsequent paper has been published which included 284 participants in a parallel arm, placebo controlled, fixed dose, randomised trial. [19] Again, participants were opioid naïve and commenced *de novo* on a sustained release formulation of morphine. Of note, not benefit was seen for the primary outcome of *breathlessness now.*

Together, these meta-analyses codify that the majority of participants in studies of morphine for the symptomatic reduction of chronic breathlessness have been (a) opioid naïve and (b)

commenced on a controlled release formulation of morphine *de novo* in the study. The evidence base from controlled clinical trials for this clinical indication is based predominantly on the use of sustained release formulations of morphine.

Currently available evidence – safety

The one systematic review and meta-analysis of safety of opioids for the symptomatic reduction in chronic breathlessness was published in 2017 by Verberkt *et al.*[20] Of note, despite the inclusion of more than 1000 participants from 63 studies, only one study of morphine to steady state included measures of all three key respiratory parameters: changes in partial pressures or saturation of oxygen, end tidal measures of carbon dioxide, and respiratory rate. [21] This was an uncontrolled study of sustained release morphine in 20 people for ten days in a crossover design, of whom twelve completed the study. There were increases in CO_2 and decreases in oxygenation, but not at levels that were clinically significant. No placebo controlled studies of immediate release oral morphine solution for the symptomatic reduction of chronic breathlessness in opioid naïve patients had these measures.

Specific tasks such as driving a motor vehicle

Prescribers need to minimise harms while maximising people's function, especially in a frail population. For example, driving is highly valued by patients and their caregivers even relatively late in the disease trajectory of a life-limiting illness. [22] A key goal of therapy in this setting then is not only reducing chronic breathlessness, but also minimising any drowsiness, poor cognition or difficulty with concentration. It is in settings such as this that the pharmacokinetics are important to consider. Lower peaks may help to minimise unwanted effects, thus allowing improved levels of function – a patient-centred value. [23] Additionally, some countries have introduced legal plasma morphine concentration limits, which need to be considered when prescribing oral morphine to a person that is still actively

driving. [24] Recommended doses of sustained release morphine for chronic breathlessness (10 – 30 mg daily) are unlikely to elevate morphine blood concentrations beyond the plasma concentration limits imposed by law, except in jurisdictions where any measurable blood level is illegal. [25,26]

In addition, the effects of improved functionality in patients should not be underestimated for their caregivers, since they provide critical support (especially when patients experience harms). [27]

Regulatory agencies

Australia has the first drug regulatory agency to licence a medication for the symptomatic reduction of chronic breathlessness. Sustained release morphine was licensed in 2019 for the symptomatic reduction of chronic breathlessness and subsidised later the same year. [28,29] Having an independent body determine that there is sufficient evidence to justify a new indication is important, moving prescribing from off-label to on-label. This allows prescribers – even if under other jurisdictions which have yet to license morphine for this indication – to work with more confidence about dose initiation and titration; there can be specific phase IV (post-marketing) surveillance of the long-term net effects of the medication; and it allows patients and the caregivers to get independently approved patient information sheets, [30] providing a level of objectivity that may not otherwise be present. Immediate release oral morphine solution was not licensed as part of this process for this indication. Of note, immediate and sustained release formulations were off patent throughout the evaluation process.

Dose frequency – patient-centred preference and the effects on compliance

Patient preference, in a number of clinical settings, is for the least frequent administration of a medication. [31-36] In at least one study in people with multiple sclerosis making treatment

decisions, such practical considerations as dose frequency ranked higher than effectiveness or side-effects of the intervention. [36]

Poor medication compliance reduces the net benefits of a therapy. Medication compliance in general averages about 50% in high income countries and is lower in chronic conditions than acute conditions. [37] Approximately half of non-compliance is not intentional, including being the result of regimens that are too complex. [37] Meta-analyses demonstrate that patients with chronic conditions requiring regular medications are more likely to be adhere to once daily administration of a medication when compared to multiple doses, [38,39] reducing non-compliance by as much as 50%. [40] It is also more likely that patients with less frequent, regular medications are more likely to take their medications on time [41] and be less likely to have an unplanned readmission. [42]

If preference is for less frequent administration, evidence shows that once-daily administration of sustained release morphine is safe and effective in reducing chronic breathlessness. [43] Doses will need to be appropriately titrated to ensure a response and get the maximum benefit. [11]

What should happen in practice?

Where available (including factors such as affordability and access), the evidence base is built strongly on controlled release formulations and this is, arguably, the choice for opioid naïve patients. Immediate release formulations can be used, but should be the choice when sustained release formulations are not available. This is particularly the case in low- or middle-income countries. Regular, low dose sustained release morphine can be commenced *de novo*, administered once daily and, when appropriately titrated, provides safe and effective reduction of chronic breathlessness.

Based on chronic pain guidelines, clinicians may be inclined to prescribe controlled release morphine formulations *together* with "as needed" immediate release formulations for episodes of more intense breathlessness (i.e. acute-on-chronic breathlessness). [44] Importantly, episodes of acute-on-chronic breathlessness are frequent, typically short in duration (less than 10 minutes), and will frequently subside before immediate-release morphine produces any relief. [45,46] As such, immediate release oral morphine is *not* recommended for episodes of acute-on-chronic breathlessness.

Implications for research

Ultimately, if clinicians would prefer to use immediate release morphine solution, then a definitive study that directly compares initiation of morphine for the symptomatic reduction of breathlessness using either a sustained release formulation or immediate release oral morphine solution in opioid-naïve patients with chronic breathlessness should be conducted. Comparable studies have been published in the palliative care of pain. Klepstad *et al* compared immediate release morphine with controlled release morphine in opioid-naïve patients who needed morphine for analgesia. [47] If there is a belief that reduction in breathlessness would be similar, then look to the immediate and short term harms (drowsiness, nausea, vomiting, impaired cognition) between the two groups [48] and power the study on harms rather than symptom reduction.

Conclusion

For clinicians, especially for those who have not prescribed opioids for chronic breathlessness, the evidence base is built predominantly around studies that have used modified release (both controlled and sustained release) formulations, not immediate release solutions including two soon-to-be-released randomised controlled trials. [4,18,49,50]

Key points

1. Both immediate release and sustained release morphine have evidence supporting their use.

2. Pharmacokinetics differ markedly between formulations, with higher peaks and lower troughs with immediate release in steady state.

3. The majority of placebo-controlled studies of morphine for the symptomatic reduction of chronic breathlessness to steady state have been carried out with low dose, sustained-release morphine.

4. Reflected across studies in a number of patient populations, once daily administration of a medication is preferred and increases adherence and thus likely clinical net benefit.

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Conflict of Interest

DCC is a paid consultant and receives payment for intellectual property with Mayne Pharma International Pty Ltd. MJJ is a paid consultant with Mayne Pharma International Pty Ltd

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