

"This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for publication in the European Respiratory Journal, prior to copy-editing, formatting and typesetting. This version of the manuscript may not be duplicated or reproduced without prior permission from the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication."

Overdosing on immediate release morphine solution has predictable adverse effects

David C Currow<sup>1,2</sup>

Magnus Ekström<sup>3</sup>

Miriam J Johnson<sup>4,5</sup>

Affiliations

<sup>1</sup> Professor of Palliative Medicine, ImPACCT, Faculty of Health, University of Technology Sydney, Ultimo, New South Wales, Australia. 2007

<sup>2</sup> Associate Director (Research), Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, England. HU6 7RX

<sup>3</sup> Department of Clinical Sciences, Division of Respiratory Medicine & Allergology, Lund University, Lund, Sweden

<sup>4</sup> Professor of Palliative Medicine, Hull York Medical School, Hull University, Cottingham Rd, Hull, England. HU6 7RX

<sup>5</sup> Director, Wolfson Palliative Care Research Centre, Hull York Medical School, Hull University, Hull, England. HU6 7RX

Corresponding author:

Professor David Currow

ImPACCT, Faculty of Health, University of Technology Sydney, New South Wales, Australia.

Email: [david.currow@uts.edu.au](mailto:david.currow@uts.edu.au)

Word count

653

References

8

Prescribing responsibility inherently includes adequate ongoing monitoring for medication.

An overdose of morphine can cause respiratory depression; as with any medication, there is a therapeutic window above which toxicities occur. Despite the increasingly widespread use of extended-release morphine for chronic breathlessness when prescribed and monitoring in line with international evidence-based recommendations, the literature is *not* replete with examples of opioid-induced respiratory depression.

Why is this case report published? [1] Morphine causes drowsiness and obtundation when an overdose is taken. In addition to his 15 mg/24 hour extended release morphine, the patient in the case report took twelve times his four hourly dose of immediate release oral morphine solution. The effects he experienced are well described toxicities on the product information for every opioid and the patient information sheets in every filled prescription. This is NOT about identifying a new danger – use morphine in an unsafe way and it will be an unsafe drug with predictable side effects. This letter therefore highlights the generic importance of good prescribing and prescribing responsibility inherently includes adequate ongoing monitoring.

The evidence base for the therapeutic clinical use of opioids in chronic breathlessness has been derived almost entirely from extended release preparations of morphine. [2,3] This choice of preparation was based on sound pharmacokinetic principles from studies done more than 20 years ago [4] and is borne out the greater effect size in aggregate data from steady state studies. [3] Even when well with no co-morbidities, anyone of us would likely experience toxicity from a *statin* dose of 30 mg of immediate release morphine solution. The goal of care is to increase the threshold at which the patient becomes breathless during exertion by adequately saturating opioid receptors and to decrease the distress caused by breathlessness in the person's life. This relies on adequate levels of background opioids. The use of *pro re nata* (PRN) immediate release oral morphine solution will increase the risk of side-effects not only because of fluctuating serum levels, but precisely because this was an overdose of immediate release morphine solution.

The approach whereby immediate release opioid is used for episodes of breathlessness (usually induced by exertion) has been transferred from pain management with empiric data in breathlessness. But, given the current evidence and knowledge about chronic breathlessness, it makes no sense to transfer a PRN IR morphine model which was not even fit for purpose in incident pain. As most episodes of exertion induced breathlessness resolve with rest within 10 minutes [5,6] no opioid preparation with a relevant pharmacokinetic profile has been studied in chronic breathlessness.

Patients need to be monitored as opioids are initiated and in follow-up in a way that is appropriate to the medication being prescribed. In settings where the medication is started during an acute exacerbation, it may be appropriate to review the person within days of discharge to explore whether they needed ongoing morphine.

The basis of the toxicity was that the man took a much higher than prescribed dose of immediate release oral morphine solution. When low dose, extended release morphine has been used in steady state, such toxicity has not been reported. Sudden changes in renal

function, or dehydration due to diarrhoea may put even people in steady state from regular, low-dose, extended release morphine at risk of harm despite a history of symptomatic benefit. Part of a pharmacist discussing regular, low-dose, extended release morphine with patients when this medication is initiated is that side effects may emerge were renal function to worsen.

Chronic breathlessness continues to be a major health problem around the world and its relief a goal of care for millions of people. [7] The most robust evidence base to date is built on the use of regular, low dose, extended release morphine. Further research into safety and titration is ongoing. Such work will be crucial to strike the therapeutic balance between maximising symptomatic benefits and minimising any likelihood of harms in these frail people. [8]

## References

1. Politis J, Le B, Smallwood N. Respiratory depression secondary to morphine use in a patient with COPD and refractory breathlessness. *Eur Resp J* 2017; 49: 1601858
2. Ekström M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax* Published Online First: 04 April 2017. doi: 10.1136/thoraxjnl-2016-209868
3. Ekstrom M, Nilsson F, Abernethy AP, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thoracic Soc* 2015; 12(7): 1079-1092.
4. Gourlay GK, Plummer JL, Cherry DA, Onley MM. A comparison of Kapanol (a new sustained-release morphine formulation), MST Continuos, and morphine solution in cancer patients: pharmacokinetic aspects of morphine and morphine metabolites. In: Gebhart GF, Hammond DL, Jensen TS, editors. *Proceedings of the 7th World Congress on Pain*. Seattle: IASP Press. 1994: 631-43.
5. Maddocks M, Taylor V, Klezlova R, England R, Manderson C, Wilcock A. When will I get my breath back? Recovery time of exercise-induced breathlessness in patients with thoracic cancer. *Lung Cancer* 2012; 76(1): 128-129.
6. Simon ST, Weingärtner V, Higginson IJ, Voltz R, Bausewein C. Definition, categorization, and terminology of episodic breathlessness: consensus by an international Delphi survey. *J Pain Symptom Manage* 2014; 47(5): 828-838
7. Currow DC, Plummer J, Crockett A, Abernethy AP. A community population survey of prevalence and severity of dyspnoea in adults. *J Pain Symptom Manage* 2009; 38(4): 533-545
8. Currow DC, Watts GJ, Johnson MJ, McDonald CF, Miners JO, Somogyi AA, Denehy L, McCaffrey N, Eckert DJ, McCloud P, Louw S, Lam L, Greene A, Fazekas B, Clark KC, Fong K, Agar M, Joshi R, Kilbreath S, Ferreira D, Ekstrom M. On behalf of the Australian National Palliative Care Clinical Studies Collaborative (PaCCSC). Study Protocol: A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic breathlessness.

The Breathlessness Exertion And Morphine Sulphate (BEAMS) Study Protocol. BMJ Open 2017.  
In press.