

Journal Watch

Relief of Incident Dyspnea in Palliative Cancer Patients: A Pilot, Randomized, Controlled Trial Comparing Nebulized Hydromorphone, Systemic Hydromorphone, and Nebulized Saline.

Margaret A. Charles, PhD, Liz Reymond, MBBS(Hons), PhD FChPM, and Fiona Israel, MCouns

Prepared by: Barry Thorneloe, PGY-1 Anesthesia Resident – Palliative Care Rotation Grey Nuns Tertiary Palliative Care Unit - September 11, 2008

Abstract

Acute episodic breathlessness in patients receiving palliative care is a distressing symptom with little evidence-base to inform management. This pilot, double-blind, controlled, crossover study compared the effects of nebulized hydromorphone, systemic hydromorphone and nebulized saline for the relief of episodic breathlessness in advanced cancer patients. On three occasions of acute breathlessness, patients randomly received either nebulized hydromorphone, a systemic breakthrough dose of hydromorphone or nebulized saline together with a blinding agent. Breathlessness was scored before and 10, 20, 30, and 60 minutes post-treatment completion using a 100 mm visual analog scale. Twenty patients completed the trial. Ratings did not differ significantly across pretest treatments. Change in ratings from pretest to 10 minutes after completion of nebulization (about 20 minutes after administration of systemic hydromorphone) indicated that each of the treatments resulted in statistically significant improvements in breathlessness, with no significant differences between treatments. Over time, breathlessness decreased significantly for all treatments, with no significant differences between treatments. Only nebulized hydromorphone produced a rapid improvement in breathlessness that reached a magnitude considered to be clinically important. Interpretation of these results is considered in relation to our definition of clinical significance, the dose of hydromorphone used and the possibility of a placebo effect. This study can serve to inform the design of future trials to investigate the management of incident breathlessness.

Strengths:

- Good methodological design: randomized, double-blinded, and placebo-controlled
 - an agent was used with normal saline nebulizer to maintain blindness
 - oral systemic doses were diluted with 20cc orange juice to disguise taste differences
- Crossover design allows for patients to experience all arms: treatments and control
- The inclusion/exclusion criteria for selected patients reflect a population of interest to palliative care physicians – cancer pain patients with uncontrolled dyspnea

- Inclusion/exclusion criteria were precise and included minimum cognition level to ensure reliable assessment of patients
- Assessments post-nebulizer (treatment and placebo arms) done at 10, 20, 30 and 60 minutes post treatment ensure adequate time to assess effect
- Test dose of hydromorphone given to ensure patient tolerance and safety
- Power calculation was done to ensure adequate sample from which to draw conclusions
- Used a modified (vertical) Visual Analog Scale (VAS) to measure degrees of dyspnea

Weaknesses:

- No intention to treat analysis
- Systemic hydromorphone doses were not equal for each patient, but calculated based on an equivalent breakthrough for the particular opioid they were on for pain ATC.
- Allow adequately powered to test for an outcome of 10% reduction in dyspnea, small sample size still limits generalizability
- if patients received no benefit from intervention, they could ask for other treatments (intention to treat) - although all other treatments recorded – could have an effect on outcome if within 60 minute time frame
- Although attempts were made to give treatments at the same time for three consecutive days, this was unrealistic and differences between arms secondary to time of day, therefore, cannot be accounted for
- Patients in “withdrawn” group not included in analysis
- Measurement of effect of systemic arm at 20 minutes may not be adequate time lapse based on pharmacokinetics and individual variation in absorption and may not be equivalent to 10 minutes post-nebulized treatment

Relevance to Palliative Care:

This paper and subject matter address cancer pain patients with opioid physical dependence and tolerance with baseline and incident dyspnea. This is a common symptom in palliative care, and one of the most difficult to treat effectively. In fact, refractory dyspnea is the second most common reason for the initiation of palliative sedation (after intractable delirium). Therefore, any new and efficacious treatments for dyspnea would be a welcome addition to the armamentarium of the palliative care physician.

However, there was no statistical difference between all arms of the study. Nebulized hydromorphone was only noted as “clinically significant” based on a pre-study definition of 10% change on the Visual Analog Scale (VAS) – [1.04]. Although the nebulized route of hydromorphone may, in theory, target opioid receptors in the alveolar wall and the smooth muscle of the trachea, the authors do not acknowledge the possibility of systemic absorption via the inhalational route making it as efficacious as hydromorphone given by other routes (IV, SC, PO).