UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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TODAY'S TOPIC:

Opioids for Terminal Dyspnea: Comparable effectiveness of opioids?

Background:

Terminal dyspnea, or shortness of breath at the end of life, is a common occurrence in patients in the last days to weeks of life. Patients most affected by this distressing symptom include those with advanced cancer, lung diseases, and heart disease. The treatment of terminal dyspnea includes both non-pharmacologic and pharmacologic interventions, depending on the etiology. In advanced cancer, parenteral opioids are recommended first-line when non-pharmacologic interventions are unsuccessful. While parenteral morphine has the most evidence in this setting, new evidence is emerging that other opioids (hydromorphone and oxycodone) have similar efficacy.

Importance:

Patients experiencing dyspnea at the end of life may benefit from treatment with parenteral opioids, and palliative care clinicians should know the data surrounding opioid use for dyspnea.

The Literature:

Cancer Med. 2023;12(5):5397-5408.

The feasibility and effects of a pharmacological treatment algorithm for cancer patients with terminal dyspnea: A multicenter cohort study

Objective: Develop and assess both the efficacy and adherence potential of an opioid-focused treatment algorithm for terminal dyspnea, or shortness of breath in the last days to weeks of life.

Methods: Visual algorithm created via literature review, discussions among researchers, and a preliminary treatment algorithm rooted in clinical practice. Patients were treated according to the developed algorithm.

- Patients were given 6-12mg per day for opioid naïve patients. Opioid-tolerant patients had their doses increased by 20-50%. Doses were then adjusted ± 20% according to clinical requirements. Medication was given as a continuous infusion.

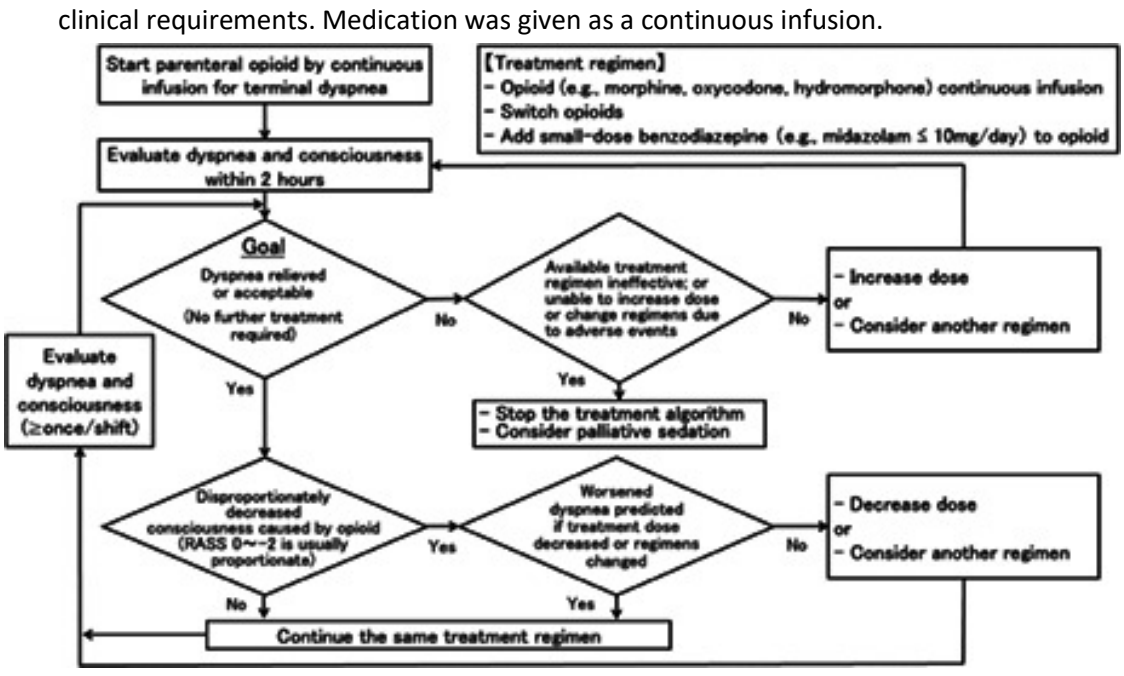

Figure 1: Treatment Algorithm

Results: n= 108

- Inclusion Criteria: Patients ≥18 years old with advanced cancer, an Eastern Cooperative Oncology Group (ECOG) performance score ≥3, moderate to overwhelming dyspnea via the Integrated Palliative care Outcomes Scale (IPOS score 2-4) and requiring continuous infusion of parenteral opioids for management.
    - Exclusion Criteria: dyspnea unrelated to cancer or scheduled to undergo interventions that would reduce dyspnea
- Dyspnea assessment via numerical rating scale (NRS) by patients and NRS and IPOS scores reported by physicians at baseline, 24, and 48 hours
- At 24 hours, 100% of patients were adherent to the treatment algorithm. At 48 hours, 94% of patients were adherent, with the other 6% discontinuing treatment via the algorithm due to adverse events and requirement of palliative sedation.

Adverse Events (CTCAE Criteria)			
Severity	Baseline (n=108)	24 hours (n=96)	48 hours (n=87)
Nausea			
1	8 (7.4%)	6 (6.3%)	3 (3.4%)
2	7 (6.5%)	0	1 (1.1%)
3	2 (1.9%)	0	0
Delirium			
1	13 (12%)	9 (9.4%)	12 (14%)
2	8 (7.4%)	9 (9.4%)	9 (10%)
3	3 (2.8%)	1 (1%)	1 (1.1%)
Apnea			
3	0	1 (1%)	1 (1.1%)

- The proportion of patients requiring benzodiazepines increased over time, with 10% of patients requiring a benzodiazepine at 48 hours.
- Patient NRS mean scores reduced from 7.3 ± 0.2 at baseline to 4.9 ± 0.3 at 24 hours and 4.6 ± 0.4 at 48 hours.
- Of the patients alive after 24 and 48 hours, 51% and 64% respectively experienced dyspnea relief (defined as IPOS ≤ 1).
- Physicians reported dyspnea was improved or much improved upon their assessment in 56% and 62% of patients at 24 and 48 hours.

Conclusion: A comprehensive treatment algorithm may be feasible, effective, and safe for treatment of terminal dyspnea in advanced cancer patients while reducing variability in practice. It can also serve as a point of reference for goals of care discussions with patients and families.

CLINICAL PEARL: Parenteral morphine, oxycodone, and hydromorphone appear to exhibit similar efficacy in terminal dyspnea relief, although clinical significance of relief is unclear based on current data.

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J Pain Symptom Manage. 2023;66(2):e177-e184.

Do Types of Opioids Matter for Terminal Cancer Dyspnea? A Preliminary Multicenter Cohort Study

Objective: Explore the safety and efficacy of parenteral morphine, oxycodone, and hydromorphone according to an established treatment algorithm (see above) for cancer patients with terminal dyspnea.

Methods: A secondary analysis of a multicenter cohort study (see above for inclusion/exclusion criteria and dosing)

- Dyspnea was assessed via IPOS score at baseline, 24, and 48 hours by physicians.

Results: n = 108

- Morphine was used in 66 (61%) of patients, oxycodone was used in 34 (32%) of patients, and hydromorphone was used in 8 (7.4%) of patients
- Among patients alive at 24 and 48 hours, no significant difference was seen in dyspnea relief (defined as IPOS score ≤ 1) (P=0.109, P=0.307).

Dyspnea Relief (IPOS ≤ 1)		
	24 hours	48 hours
Morphine	35/60 (58%)	37/54 (69%)
Oxycodone	11/31 (36%)	14/27 (52%)
Hydromorphone	3/5 (60%)	4/5 (80%)

Dyspnea Relief Based on IPOS Scores		
	24 hours	48 hours
IPOS ≤ 1	49/96 (51%)	55/86 (63.9%)

- No significant difference found in median IPOS score among the 3 groups at 24 (P=0.08) and 48 (P=0.322) hours.

IPOS Scores			
	Baseline	24 hours	48 hours
Morphine	3.0 ± 0.1	1.6 ± 0.1	1.4 ± 0.1
Oxycodone	2.9 ± 0.1	2.0 ± 0.2	1.6 ± 0.2
Hydromorphone	3.5 ± 0.2	1.2 ± 0.4	1.2 ± 0.2

- No significant difference was found in goals of dyspnea relief (defined as the case where dyspnea is alleviated or is acceptable to the patient)

Goals of Dyspnea Relief		
	24 Hours	48 hours
Morphine	42/60 (70%)	42/53 (78%)
Oxycodone	19/31 (61%)	17/27 (63%)
Hydromorphone	5/5 (100%)	5/5 (100%)

- Adverse events were mild to moderate (CTCAE grade 1-2) and included nausea and delirium. No significant difference was found among the 3 treatment groups.

Conclusions: Morphine, oxycodone, and hydromorphone exhibited reduction in dyspnea intensity when utilized according to a standardized algorithm, without significant differences between groups in efficacy or safety.

Study Critiques:

- Neither of these studies reported the proportion of patients who required an increased or decreased opioid dose for further dyspnea control. This data would be important to know in order to determine the most appropriate dose of each opioid, given the opioids did not seem to influence dyspnea scores after the 24 hour mark.
- Recording dyspnea data at 24 and 48 hours is not ideal in this end of lie scenario. Intravenous opioids reach peak concentration within 20 minutes of administration, and a continuous infusion will reach steady state within 8-12 hours. Obtaining IPOS scores at shorter intervals such as every 8 or 12 hours may have been a more useful reflection of efficacy in this patient population.
- Very small sample size, particularly for the hydromorphone group, undermining both the internal and external validity of the study.

Bottom Line:

- In advanced cancer in particular, parenteral opioids appear to be effective in providing dyspnea relief about 50% of the time.
- Parenteral morphine, oxycodone, and hydromorphone appear to exhibit similar efficacy and safety in this patient population.
    - NOTE: parenteral oxycodone is not available in the US. These results may not extend to oral oxycodone, and professionals should continue to select opioids based on individual patient factors.
- While the above results are statistically significant, the clinical benefit is still unclear, and additional randomized controlled trials are needed to confirm preliminary findings.
- A continuous infusion of morphine, oxycodone, or hydromorphone was effective in reducing terminal dyspnea in ~50% of patients after 24 hours of treatment, with the majority of patients tolerating the expected side effects of opioids. Therefore, these agents may be used with caution in advanced cancer patients with terminal dyspnea.

CLINICAL PEARL: Parenteral morphine, oxycodone, and hydromorphone appear to exhibit similar efficacy in terminal dyspnea relief, although clinical significance of relief is unclear based on current data.