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Respiratory function during parenteral opioid titration for cancer pain

Bassam Estfan, **Fade Mahmoud**, **Philip Shaheen**, **Mellar P Davis**, **Wael Lasheen**, **Nilo Rivera**, **Susan B LeGrand, Ruth L Lagman** The Harry R. Horvitz Center for Palliative Medicine* and The Taussig Cancer Center **Declan Walsh** and **Lisa Rybicki** Department of Quantitative Health Sciences, The Cleveland Clinic Foundation

Background: Respiratory depression is the most feared opioid-related side-effect yet research on the topic is sparse. We evaluated changes in respiratory parameters during parenteral opioid titration for cancer pain to determine if opioid titration was associated with evidence of hypoventilation. The primary outcome measure was to measure changes in end-tidal CO_2 (ET-CO_2) during opioid titration to pain control. **Methods:** Subjects with severe cancer pain admitted for parenteral opioid titration for poorly controlled pain were eligible. Those who were oxygen dependent were excluded. ET-CO_2, O_2 saturation, respiratory rate (RR), and vital signs were monitored daily until pain control was achieved. **Results:** 30 patients completed the study of which 29 are reported. The mean ET-CO_2 at initial evaluation was 33.3 ± 5.0 and 34.7 ± 5.7 mmHg at pain control ($P = 0.14$, 95% CI -0.5 to 3.3). None had an ET-CO_2 ≥ 50 mmHg. All maintained O_2 saturation $\geq 92\%$. RR dropped transiently below 10/minute in two subjects. **Conclusions:** Parenteral opioid titration for relief of cancer pain was not associated with respiratory depression as demonstrated by significant changes in ET-CO_2 or oxygen saturation in non-oxygen dependent cancer patients. *Palliative Medicine* 2007; **21:** 81–86

Key words: cancer; carbon dioxide; opioids; oxygen; pain; respiratory

Introduction

Opioids are the mainstay for moderate to severe cancer pain management.[1] Although 80–90% of cancer pain can be controlled with opioids, suboptimal pain control is common because under-prescribing remains a major barrier.[2] Concerns regarding adverse effects are one of the important physician barriers to aggressive opioid titration. Physicians are concerned about drug abuse, diversion, hemodynamic instability, central nervous system (CNS) toxicity, and most importantly respiratory depression. Deaths from opioid over-dose or abuse are usually attributed to respiratory depression.[3]

Few studies have addressed objective changes in respiration and gas exchange during opioid titration in cancer.[4–7] Paradoxically most[5–7] have addressed opioid use for dyspnea although this is a less frequent indication. The relationship between opioids and respiratory depression has also been studied in healthy volunteers without pain and in post-surgical patients.[8,9] Most were opioid-naïve, or had acute pain that required intermittent opioid dosing but not the aggressive dose titration or long term use of opioids used for cancer pain. Interpretation of these studies is also complex due to variations in the definitions of respiratory depression used.[8,9]

Cancer patients frequently have co-morbidities, which could potentially adversely influence gas exchange. These include pulmonary metastases, pleural effusions, chronic obstructive lung disease (COPD), heart failure (CHF) and pulmonary embolism. They may complicate or potentiate adverse opioid respiratory effects. Adherence to proper and safe opioid prescribing is rarely associated with clinically recognized respiratory depression.[10] One study at steady-state following oral morphine use for cancer pain in hospice patients found no significant evidence of ventilatory failure.[4]

Patients admitted to the hospital for urgent pain control and given intravenous opioids might be considered to be at greatest risk of respiratory depression. We hypothesized that proper opioid titration is not associated with clinically significant respiratory depression nor significant adverse respiratory effects as determined by serial measurements of respiratory rate, end-tidal carbon dioxide (ET-CO_2) and oxygen saturation. In this study we assessed respiratory function

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Address for correspondence: Declan Walsh, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk M76, Cleveland, OH 44195, USA. E-mail: walsht@ccf.org

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and adequacy of ventilation in non-oxygen dependent patients during opioid titration to pain control for cancer pain.

Methods

Patient selection

Cancer patients admitted to an inpatient palliative medicine acute care unit were evaluated for eligibility if they required parenteral opioids for pain. Both opioid naïve and opioid tolerant individuals were included. Inclusion criteria were: (1) age > 18 years; (2) active cancer; (3) cancer pain necessitating continuous parenteral opioid infusion; and (4) capable and willing to sign informed consent. Exclusion criteria: (1) home oxygen prior to admission or oxygen supplementation during opioid titration; (2) use of parenteral opioids prior to study; (3) delirium as determined by a score ≥ 3 on the Bedside Confusion Scale (0–4) which is a validated simple and quick clinical measure of delirium; (4) unable to understand English; and (5) refused participation. Those admitted at night or on weekends were not included as timely proper consent and ET-CO_2 could not be obtained prior to the urgent need to start parenteral opioids. The Cleveland Clinic Institutional Review Board (IRB) approved this study.

Data collection

Baseline data collection were always conducted prior to initiation of continuous opioid infusion and included: (1) demographic information (age, gender, and race); (2) diagnosis, extent of disease, pulmonary and cardiac comorbidities, social history, and Eastern Cooperative Oncology Group (ECOG) performance score which rates performance status on a (best–worst) 0–4 scale; (3) social history—including smoking; (4) dyspnea severity on an 11-point numerical rating scale (NRS) where 0 is none and 10 severe dyspnea; (5) current oral opioids—if any; (6) pain characteristics (site, type, and severity on an 11-point NRS where 0 is none and 10 severe pain); (7) vital signs; (8) Bedside Confusion Scale score; and (9) ET-CO_2 plus oxygen saturation.[12–14]

Daily data collection included pain and dyspnea severity, vital signs, Bedside Confusion Scale score, ET-CO_2, oxygen saturation, opioid dose and medication changes. Assessments were attempted at the same time daily (usually in the morning). All measurements were obtained no less than 2 hours after the last opioid breakthrough dose to minimize the effect of an isolated opioid rescue dose on ET-CO_2, respiratory rate (RR), and oxygen saturation.

Respiratory parameters

A Nellcor® capnometer (Nellcor, Pleasanton, CA) was utilized to measure ET-CO_2, RR, pulse, and oxygen saturation. Blood pressure and temperature values were taken from standard nursing charts. Measurements were done after patients were lying supine for at least 10 minutes.

Completion and withdrawal criteria

Patients either completed the study once pain control was obtained or were classified as withdrawn. Pain control was defined as (a) a score of 4 or less on a pain NRS and (b) 4 or less breakthrough opioid doses within the previous 24 hours (for non-incident pain). They were withdrawn if they: (1) had intercurrent disease complications precluding continuation; (2) required oxygen therapy; (3) were switched to as needed (PRN) or oral opioid prior to achieving pain control; (4) withdrew consent; and (5) became delirious.

Respiratory monitoring

If hypoxia (oxygen saturation <90 mmHg) or hypercapnia (ET-CO_2 $\geq$50 mmHg) developed, a comprehensive global clinical evaluation would assess the etiology and determine management. If ET-CO_2 was above 50 mmHg at any time it would be reconfirmed after 30 minutes. If persistently elevated an arterial blood gas (ABG) sampling would then be obtained as clinically indicated.

Study end-points

The primary end point was the change in ET-CO_2 between initiation of opioid titration and pain control. Secondary variables included changes in respiratory rate, oxygen saturation, clinical respiratory depression, sedation, delirium, and the need for ABGs.

Statistical analysis

Patient characteristics were summarized as frequencies and percentages, or as the mean, standard deviation, median, and range. The change in ET-CO_2 from baseline to the last day was analyzed using paired t-tests. A 95% CI was also calculated to estimate ET-CO_2 changes. The goal was to include 30 evaluable patients to assure an 83% power to detect a mean change of 4 mmHg in ET-CO_2 using a 5% level of significance.

Results

Between April 2003 and June 2004, 129 consecutive patients met the enrollment criteria. Two refused to participate, two were delirious at presentation, and seven excluded for other reasons. Seventy-two could not be evaluated before starting an opioid infusion, e.g. because of being admitted during night hours or weekends. Of the

remaining 46 who provided consent, seven had incomplete data, nine were withdrawn during this study for various reasons, including six who developed delirium, one at the attending physician's discretion, one withdrew consent, and one was changed to intermittent opioid dosing. Thirty consecutive patients completed the study. One of the thirty (#10) had incomplete data for the final day of the study and accordingly was removed from the final analysis.

Patient characteristics are in Table 1. The median age was 60 years (range 29–85). Male:female ratio was 1:1.3. Gastrointestinal primary sites were the most prevalent cancers followed by genitourinary malignancies. Two had lung cancer. Fourteen had known metastases; 18 had poor performance status defined as an ECOG score of 3 or 4. Four had concomitant pulmonary disease (one each bronchitis, asthma, pleural effusion, and radiation pneumonitis). Of those on opioids before the study, 13 were on morphine, six on fentanyl, four on oxycodone, and one each on methadone and hydromorphone. Five were opioid-naïve. Patients were on study for a median of 3 days (range 2–10).

The mean pain scores changed from 6.8 ± 2 at baseline to 1.9 ± 1.3 at study completion ($n = 29$). The median oral morphine equivalent daily dose (MEDD) for those evaluable was 73 ± 94 mg (range: 0–300) at baseline and 169 ± 160 mg (range: 72–720) at completion ($n = 29$). One went from an oral morphine equivalent daily dose of 300 to 21600 mg at the completion of study and as an outlier was excluded only from the mean opioid dose calculations. Oral opioid doses prior to parenteral infusion were unavailable in seven. Patients 8 and 23 had improper labeling of initial opioid dosage; patients 12, 17 and 18 were on an unknown dose of as needed opioid prior to study; patient 30 was initially on methadone and conversion to MEDD could not be done; patient 10 was excluded from data analysis for the reason mentioned earlier. Twenty-six received morphine; two each fentanyl and hydromorphone opioid infusions. Further titration from the initial basal continuous infusion rate chosen was necessary in 11; nineteen did not need further dose titration. In those evaluable, and not opioid-naïve the calculated equianalgesic continuous parenteral opioid dosage was larger than the baseline oral opioid dosage.

Mean ET-CO_2 (Figures 1 and 2) changed from 33.3 ± 5.0 mmHg (range: 26–44) at baseline to 34.7 ± 5.7 mmHg (range: 22–47) at pain control ($n = 29$). The 95% CI for

Table 1 Patient characteristics ($n = 30$ who completed all study requirements)

Patient	Age	Gender	PS	BSC	Primary site	Extent of disease
1	44	F	3	0	Gastric	Local
2	39	M	1	0	Esophageal	Liver
3	63	F	3	2	Colon	Liver, ovaries
4	66	F	2	1	Pancreas	Liver, lung, peritoneum
5	64	M	0	0	Lung	Bone
6	54	F	1	1	Unknown	Lung
7	42	M	3	0	Sarcoma	Local
8	46	M	3	1	Esophagus	Local
9	43	F	1	0	Colon	Local
10*	74	F	2	0	Pancreas	Local
11	85	F	3	2	Lymphoma	N/A
12	56	M	3	1	Lung	Local
13	66	M	2	0	Bladder	Bone
14	62	M	3	0	Kidney	Local
15	58	F	3	0	Myeloma	Local
16	58	M	3	0	Rectum	Local
17	66	F	3	2	Unknown	Local
18	74	M	3	0	Prostate	Bone
19	37	F	4	0	Unknown	Bone, lung, LN
20	56	F	2	0	Breast	Bone, liver, LN
21	48	F	2	0	Breast	LN
22	64	M	3	0	Cervix	Local
23	81	M	3	2	Bladder	Local
24	74	F	3	0	Kidney	Local
25	53	F	3	0	Myeloma	Bone
26	36	F	3	1	Breast	Bone, LN
27	64	M	0	0	Tongue	Local
28	62	F	3	0	Kidney	Local
29	75	F	2	1	Unknown	Bone
30	29	M	3	0	Sarcoma	Bone, lung

BSC: Bedside Confusion scale, F: female, LN: lymph nodes, M: male, PS: performance status.
*Patient #10 was excluded from the final analysis (see text).

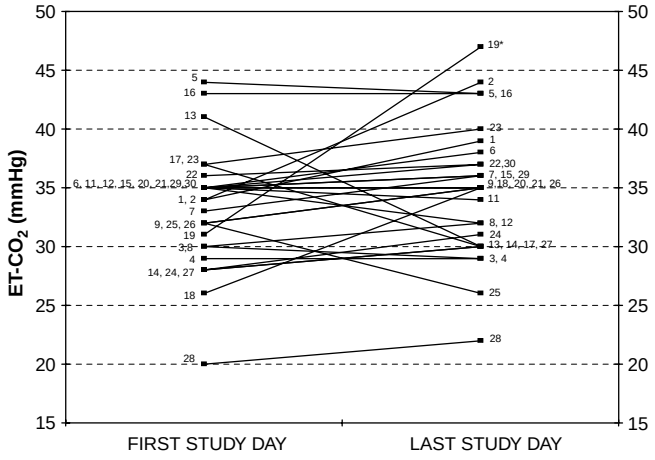

Figure 1 ET-CO_2 changes in individual patients. Numbers represent individual study subjects ($n = 29$).

differences in ET-CO_2 from baseline to last day was between -0.5 and 3.3 mmHg. The mean increase in ET-CO_2 at completion (1.4 mmHg above baseline) was not statistically significant ($P = 0.14$). Four increased ET-CO_2 >4 mmHg from baseline (5, 9, 10, and 16 mmHg, respectively); two of these had been opioid-naïve, and another two had a simultaneous decrease in RR (Table 2). Four decreased ET- CO_2 >4 mmHg at completion. ET-CO_2 never exceeded 50 mmHg in all who completed the study. Oxygen saturation remained above 92% in all throughout. No patient required further respiratory evaluation, including ABG due to hypercapnia or hypoxia. Respiratory rate remained above 10/minute except in the two who had a transient drop in RR to 8 and 9 per minute (patients #19 and 5, respectively) one of whom was opioid-naïve. This recovered spontaneously without dose modification and subsequently remained above 10 per minute until study completion. None manifested clinically significant respiratory depression necessitating opioid discontinuation or dose reduction (including those who had ET-CO_2 changes >4 mmHg or a transient decrease in RR). None of those withdrawn because of delirium had ET-CO_2 >40 mmHg or O_2 sat <89 mmHg before the onset.

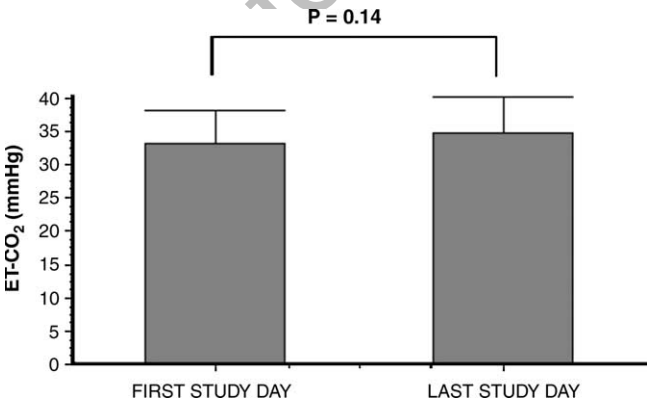

Figure 2 Mean and standard deviation of ET-CO_2 on the first and last study days ($n = 29$).

Discussion

Despite the many concerns about respiratory depression with opioids in the general cancer or surgical populations, few studies have been done particularly during opioid titration in cancer pain. In our practice[10] we titrate parenteral opioid doses for cancer pain without specific regard to age, race, underlying malignancy or respiratory illnesses. The purpose of this study was to evaluate respiratory function in those with chronic severe pain, rather than in dyspnea or short-lived pain syndromes. It was an observational study of our current standard of care. We excluded those dependent on oxygen to ensure a reasonably homogenous population. To evaluate hypoxia and hypercapnia (as determined by ET-CO_2), would also have been more difficult if supplemental oxygen were in use.

Respiratory depression can be defined as: (1) increased arterial CO_2; (2) decreased arterial O_2; (3) decreased RR (4) decreased tidal volume; and (5) decreased ventilatory response to hypercapnia.[8] The definition must consider both clinical and objective measures. Examples of clinical measures suggestive of respiratory depression include perceived shallow or insufficient breathing, cyanosis, and mental clouding. Tidal volume and response to hypercapnia cannot be conveniently measured at the bedside. We used ET-CO_2, O_2 saturation, and RR changes to measure respiratory function. ET-CO_2 was selected as a primary measured variable. It is directly influenced by alveolar gas exchange, and better reflects effective ventilatory exchange than either tidal volume or RR. ABGs remain the gold standard for measuring CO_2. Nevertheless, ABGs are invasive and painful especially when repeated. Furthermore, the IRB did not permit serial or episodic CO_2 monitoring by ABG.

ET-CO_2 is a non-invasive alternative to ABGs and detects CO_2 changes in real time.[12–14] ET-CO_2 correlates well with arterial blood gases in non-intubated patients. They are usually 3.5 mmHg lower than results by ABG.[12–14] Only one patient ever had an ET-CO_2 of 47 mmHg, which potentially could have reflected an ABG measurement above 50. ET-CO_2 may be misleading (falsely low) in heart failure; none of our patients had a clinical history of heart failure. Mean ET-CO_2 did not differ significantly from the first to last day. The coefficient of variation by repeat testing was 4 mmHg; however even by excluding this, e.g. a variation of 0, there was no significant change in ET-CO_2. This supports the premise that appropriate titration of opioids to pain control is not associated with respiratory depression nor a major concern during titration in those who do

Table 2 Subjects with ET-CO_2 change >4 mmHg

Patient	ET-CO_2 Δ (range) (mmHg)	RR change	First MEDD (mg)	Last MEDD (mg)	Pulmonary disorder
1	5 (34–39)	0	0	140	None
2	10 (34–44)	0	135	192	None
18	9 (26–35)	−5	0	72	None
19	16 (31–47)	−10	300	21 600	Small pleural effusion

ET-CO_2: end-tidal CO_2, MEDD: morphine oral equivalent daily dose, RR: respiratory rate.

not require oxygen. Pain control was achieved in a relatively short time (median 3 days). There was a twofold difference between initial and final MEDD for those completing the study suggesting aggressive opioid titration. Pain is a natural antagonist to opioid respiratory depression.[15] Opioid induced depression can occur after unexpected sudden pain relief even on stable opioid doses.[16,17] Gas exchange need not be monitored when opioids are titrated to pain control, provided opioids are used carefully and correctly, and patients at risk are carefully monitored.

In one study, RR, pulse, blood pressure and ABGs were monitored during intravenous morphine titration (2–5 mg every 10 minutes) in 15 patients with cancer pain.[11] A minority had a 20% transient decrease in P_AO_2 or increase in P_ACO_2 during the first 24 hours of IV opioid use, but did not require dose reduction. The increase in ET-CO_2 in the four patients in our study was similar.[10] Interestingly, ET-CO_2 also decreased in another four during titration in our study. Pain relief may allow better ventilation by reducing the pain associated with the movement involved in breathing. Our study differed in the larger number of patients studied, the method of opioid dose titration and a longer time on study; the conclusions from both studies are similar. We did not specify an evaluation algorithm in our protocol for those who decreased RR. Although two had transient drops in RR below 10 minutes, they did not have concomitant hypercapnia or hypoxia or mental clouding suggestive of impending respiratory depression. They were clinically monitored by the nursing staff. Neither had expressed clinical or objective signs of respiratory compromise before or after.

The limitations of our study were perhaps the exclusion of oxygen dependent subjects (although we believe that there was a good reason to do this) and the single daily measurement to assess respiratory function. We did not measure ET-CO_2 in those who became delirious at the point this developed during the course of the study and may have missed hypercapnia as a cause. Hypercapnia may be unrelated to steady state opioid levels. We could not exclude transient hypercapnia, or hypoxia occurring between the daily ET-CO_2 measurements. Continuous monitoring of ET-CO_2 or multiple daily measurements would have strengthened the study. A minority of those eligible were enrolled (23%); this may reduce the generalizability of our results. Future research should focus on gas exchange in those on stable opioid doses, serial measures of respiratory function, including those who are oxygen dependent or who are on opioids for dyspnea.

Conclusions

Titration of parenteral opioids for relief of moderate to severe cancer pain was not associated with clinical or objective evidence of respiration depression. Gas exchange need not be monitored routinely when parenteral opioids are titrated to pain control.

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