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Continuous Monitoring Detected Respiratory Depressive Episodes in Proximity to Adverse Respiratory Events During the PRODIGY Trial

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Purpose: The PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial was a multicenter prospective trial conducted to develop a risk prediction score for opioid-induced respiratory depressive (OIRD) episodes. Several subjects in the PRODIGY trial developed critical respiratory depressive events, which were qualified as reportable adverse events (AEs). In this study, we determine whether those patients also had an episode of OIRD as detected by continuous capnography and pulse oximetry leading up to the critical clinical event.

Methods: Blinded capnography and pulse oximetry data from PRODIGY patients who had critical respiratory depressive AE were reviewed. The occurrence and timing of OIRD episodes were recorded in relationship to the AE.

Results: Of the 1335 subjects in PRODIGY, 7 patients had 8 reportable pulmonary AE and 187 OIRDs (150 apnea episodes, 14 bradypnea episodes, 23 hypoxic episodes) with median 12 (5–19.5) OIRDs per patient. Five patients were monitored before the AE, and multiple preceding OIRD episodes were detected. One patient had 2 AE, the first (hypoxemia) was recognized upon application of pulse oximetry. This patient subsequently had multiple OIRDs until the second AE occurred (somnia requiring naloxone administration). Another patient's AE (hypotension and bradypnea) was recognized upon monitor application and subsequently had many OIRD episodes.

Conclusions: In the PRODIGY trial, patients who had a pulmonary AE had multiple preceding OIRDs detected by continuous capnography and pulse oximetry. When monitoring was initiated before the AE, numerous OIRDs, mostly apneic episodes preceded AE, suggesting continuous monitoring of both ventilation and oxygenation may allow for early detection and possible prediction of future clinical decompensation.

Key Words: respiratory depression, opioid analgesia, capnography

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Opioid induced respiratory depression (OIRD) can deteriorate into acute respiratory failure and consequent anoxic brain injury or death.¹ Recent evidence suggests that OIRD is common in postoperative patients.^{2,3} Sun et al³ demonstrated that hypoxemia as detected by blinded continuous pulse oximetry occurred in as many as 37% of patients on general care wards. Routine monitoring missed up to 90% of these episodes.³ The PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) study, a prospective observational trial where 1335 patients on general care wards were monitored by continuous capnography and pulse oximetry, found that 46% of patients had an episode of monitor detected OIRD.² A recent secondary analysis of PRODIGY by Driver et al⁴ found that most patients who had OIRD had multiple episodes.

Although these studies found that OIRD detected by continuous monitoring is frequent on the hospital general care floor, more serious episodes (critical clinical events) of OIRD are rare. Two studies from the Mayo Clinic, which relied on naloxone administration on general care wards as a proxy for severe OIRD, found that incidence of naloxone administration was 1.2 to 1.6 per 1000 postsurgical patients on general care wards.^{5,6} Thus, despite the size of PRODIGY, it was still underpowered to determine risk for more serious, but infrequent, OIRD adverse events (AEs). However, several patients in PRODIGY developed critical respiratory depressive events, which qualified as reportable AEs while they were being monitored. This provides a unique opportunity to review continuous capnography and pulse oximetry data that surround these AEs. In this study, we reviewed these data with the aim of describing continuously collected capnography and pulse oximetry data in those patients who had a critical respiratory depressive AE.

METHODS AND MATERIALS

Study Background

PRODIGY (prospective trial conducted between April 2017 and May 2018 at 16 sites in 7 countries) was approved by appropriate institutional review boards, and written informed consent was obtained from all subjects (subjects included adults [≥18, 20, and 21 y in the United States/Europe, Japan, and Singapore, respectively]) before enrollment. The trial was registered before patient enrollment at clinicaltrials.gov (NCT02811302).² Subjects were 1335 surgical and medical patients receiving parenteral opioids on the general care floor and were continuously monitored by pulse oximetry and capnography (Capnostream 20p or 35; Medtronic, Boulder, CO) for up to 48 hours.² Output from the monitor was blinded and patients underwent standard monitoring. Expired carbon dioxide values were used to calculate respiratory rate. These readings were subsequently interrogated for potential episodes of OIRD (defined as respiratory rate ≤5 breaths per minute for ≥3 minutes; SpO₂ ≤85% for ≥3 minutes; ET-CO₂ ≤ 15 or

≥60 mm Hg for ≥3 minutes; apnea episode >30 seconds).² These potential OIRD episodes were then manually reviewed by an independent Clinical Event Committee and adjudicated as OIRD or artifact or RD but not related to opioids. The primary objective was to derive an OIRD risk prediction tool (PRODIGY score).² The PRODIGY score uses 5 clinical factors (age >60 in decades, male sex, sleep-disordered breathing, opioid naivety, and chronic heart failure), assigning patients to low (<8), intermediate (8–15), or high risk (>15) for the risk of OIRD episodes. In addition to OIRD episodes, AEs (defined by ISO 14155:2011—any untoward medical occurrence, unintended disease or injury, or untoward clinical signs) were recorded and reviewed by the clinical event committee. Anticipated respiratory opioid-related AEs included but were not limited to: narcotic overdose that required opioid reversal, partial airway obstruction that required an neuromuscular blocking agent antagonist, respiratory insufficiency that required noninvasive positive pressure ventilation, respiratory failure requiring invasive mechanical ventilation, respiratory challenges leading to transfer to the intensive care unit, cardiopulmonary arrest, and death.²

Study Design

In this post hoc study, those patients who had a critical respiratory depressive AE were identified. Capnography and pulse oximetry of these patients were manually reviewed (J.J.K., T.N.W.) to adjudicate potential OIRD as actual episodes or artifact. A “potential” episode of OIRD that met the threshold deviation criteria specified previously only became “confirmed” if the monitor tracings were consistent with physiologic and clinical findings in the

record, thus eliminating OIRD episodes that may have been artifact due to patient movement, dislodging of the transducer, or other common reasons for artifact. In this post hoc analysis, all potential OIRD episodes were adjudicated, and the number, time and type of actual episodes were recorded. Categorical and continuous variables were described using counts and percentages and median and interquartile ranges, respectively.

RESULTS

Seven PRODIGY patients had 8 reportable critical respiratory depressive AEs (Table 1), which represented 0.5% of the entire PRODIGY cohort (7 of 1335 subjects yielding an incidence of 6.0 [95% confidence interval, 2.3–11.0] per 1000 patients). These patients’ medical histories were comparable with the entire PRODIGY cohort, with a distribution of the American Society of Anesthesiologists physical status score, body mass index, length of surgery, and postprocedure opioid dosage similar to the overall trial cohort. Common comorbidities included hypertension, history of smoking, asthma, and chronic pain.^{2,7}

There were 187 episodes (150 apnea [Fig. 1], 14 bradypnea, 23 hypoxic episodes [Fig. 2]) with median 12 (5–19.5) episodes per patient. Five were monitored before the AE, and multiple preceding respiratory depressive episodes were detected. Patient 6 had 2 AEs, and the first (hypoxemia) was recognized upon monitor application. This patient subsequently had multiple respiratory depressive episodes until the second AE occurred (somnolence as recognized by the clinician and requiring naloxone administration). Patient 7’s AE (hypotension and bradypnea) was also recognized

TABLE 1. Summary of AEs From Pulmonary Causes and OIRD Episodes Detected by Blinded Continuous Respiratory Monitoring

Patient #, Age (y), Sex	PRODIGY Score	Surgery	Adverse Event	Monitoring Duration, h	Monitoring Initiated	OIRD Episodes
1. 46, F	Low	General	Bradypnea	22.4	Before event	T = 16 A = 16 H = 0 D = 0
2. 81, M	High	Orthopedic	Hypoxemia	30.5	Before event	T = 121 A = 103 H = 11 D = 7
3. 63, F	High	Gynecology	Hypoxemia	24.2	Before event	T = 5 A = 5 H = 0 D = 0
4. 68, M	High	General	Hypoxemia	24.0	Before event	T = 5 A = 4 H = 1 D = 0
5. 60, F	High	General	Hypoxemia	24.6	Before event	T = 12 A = 11 H = 0 D = 1
6. 75, F	High	Medical	1. Hypoxemia 2. Somnolence	26.9	1. During event 2. Before event	T = 23 A = 8 H = 0 D = 15
7. 64, F	Intermediate	Orthopedic	Hypotension and bradypnea	19.3	During event	T = 5 A = 3 H = 2 D = 0

A, apnea (episode lasting >30 seconds); D, oxyhemoglobin desaturation (oxygen saturation ≤ 85% for ≥3 minutes); H, hypopnea (respiratory rate ≤5 breaths per minute for 3 minutes); T, total.

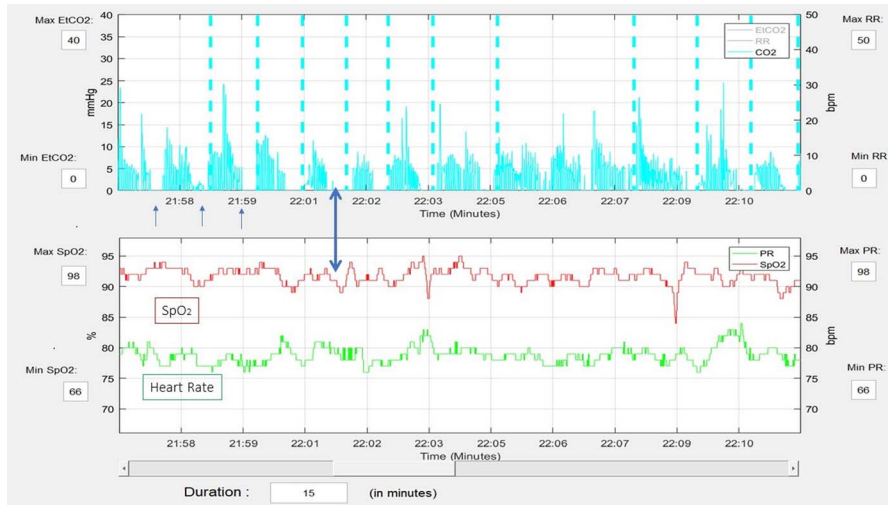


FIGURE 1. Observed respiratory depressive episodes from continuous capnography and pulse oximetry in patient 2. The top panel is expired carbon dioxide and blue dashed lines represent apneic episode alarms. The bottom panel depicts oxyhemoglobin saturation in red and heart rate in green. Single arrows show apneic episodes before recording of the AE. Bidirectional arrow shows the apneic episode with corresponding hypoxemia at the time of the recorded AE.

upon monitor application, and this patient had multiple subsequent respiratory depressive episodes. The patient exhibited mild hypotension concurrent with nausea and dizziness, along with a respiratory rate of 7 to 9 breaths per minute in the 5 minutes immediately preceding the AE.

DISCUSSION

In this analysis of the subset of PRODIGY trial patients who had a reportable critical respiratory depressive AE, the important finding was that they all had multiple respiratory depressive episodes (and a majority of these preceded the AE) recorded by continuous capnography and pulse oximetry while hospitalized on standard wards. The OIRD episodes were characterized by various presentations; however, apneic episodes exceeded all other presentations. Therefore, events recorded by capnography in our patients with severe AE exceeded predictive value of oxy-

hemoglobin monitoring as a warning sign of impending respiratory complication. Furthermore, 5 of 7 patients had a high-risk PRODIGY score suggesting validity of this score in predicting adverse respiratory events.

Our findings were similar to those of Driver et al⁴ where it was observed that OIRD episodes were rarely isolated and that patients with high-risk score for OIRD (high PRODIGY score) had median of 5 episodes per patients compared with 0 and 1 for patients with low- and intermediate-risk PRODIGY scores. The median number of episodes in our small cohort was 12, suggesting that patients who have multiple respiratory depressive episodes detected by capnography warrant immediate evaluation and perhaps intervention. Recently, Chung et al⁸ used capnography and pulse oximetry to characterize OIRD in the postanesthesia care unit (PACU) and found that these episodes are common and repetitive. Similarly, but using a different monitoring technology (pulse oximetry without capnography), Sun et al³ found that nearly 40%

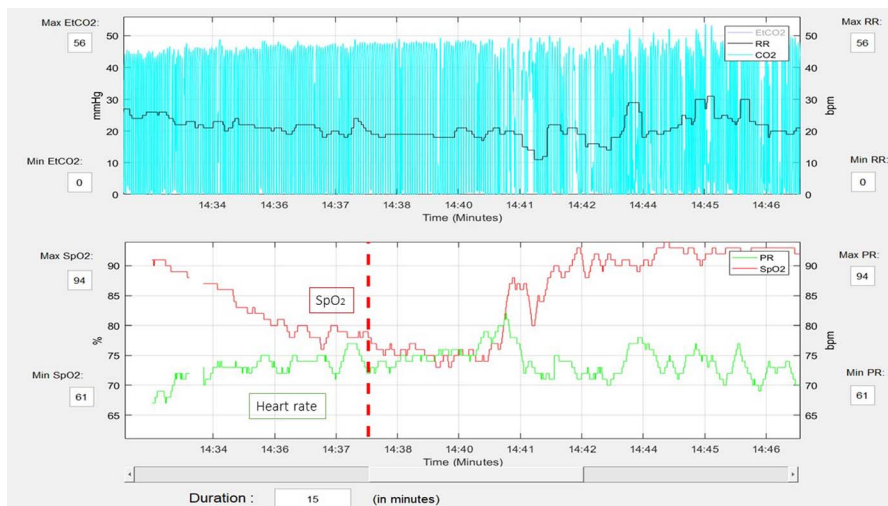


FIGURE 2. Observed hypoxemia in patient 5 which triggered the reporting of an AE for hypoxemia. The top panel is expired carbon dioxide and the bottom panel depicts oxyhemoglobin saturation in red and heart rate in green. The red dashed line represents a hypoxemia episode alarm.

of postoperative patients on general care wards had an episode of hypoxemia, which occurred for at least 1 hour. The results of the PRODIGY trial² and Sun et al³ study demonstrate that OIRD is common and underappreciated by intermittent spot vital sign checks.

The observation that respiratory depressive episodes preceded the AE is consistent with the experience at the Mayo Clinic. In that practice, postoperative patients admitted to the PACU are continuously monitored for signs of respiratory depression, and if detected have their anesthesia recovery prolonged, discharged with continuous monitoring, and/or have application of noninvasive positive airway pressure devices.⁹ Despite these safeguards, 2 studies from Mayo Clinic found that patients who had a single episode of respiratory depression in the PACU had a 5-fold increased risk of requiring naloxone on the standard care wards to reverse severe opioid toxicity.^{5,6} Similarly, Chung et al⁸ used capnography and pulse oximetry in the PACU to detect respiratory AEs, which detected these events much earlier (average, 8 minutes) before they were detected by routine clinical monitoring. Numerous studies have found that early signs of physiologic instability manifest before profound deterioration leading to a critical event.¹⁰ As the number of prearrest abnormal vital signs increases, so does the chance of postarrest mortality.¹¹ The observations in this current study as well as studies of postoperative naloxone administration^{5,6} suggest self-limited episodes of respiratory depression represent such early signs of instability and that a patient who is repeatedly setting of an alarm needs attention.

This study has several limitations. Because continuous monitoring in PRODIGY was blinded and patients were managed by routine monitoring, there is the strong possibility that some patients had unrecognized dangerous degrees of respiratory depression, which, fortunately, spontaneously corrected. Reliance on routine clinical monitoring, which has low sensitivity to detect serious respiratory depressive events, explains the low rate of AEs. Finally, our conclusions based on reported cases may be biased by the fact that they all had severe respiratory AE, and it is expected that cardiorespiratory monitors detect OIRD episodes.

CONCLUSIONS

Our patient series demonstrated that severe respiratory AEs were preceded by multiple OIRD episodes, which may be detected with continuous monitoring that provides detailed ventilation/oxygenation information compared with oxyhemoglobin saturation only. Specifically, the most important finding was that apneic episodes detected with capnography, rather than hypoxemia, were the most prominent OIRD sign preceding pulmonary AE in our patients. These observations may provide the necessary pilot data for the development of a much-needed large interventional trial where

interventions in response to continuous oximetry and capnography monitoring episodes. Such a trial could test the hypothesis that early intervention on patients having numerous OIRD episodes detected by capnography and pulse oximetry could reduce the risk of serious life-threatening respiratory AE events.

REFERENCES

1. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*. 2015;122:659–665.
2. Khanna AK, Bergese SD, Jungquist CR, et al. Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: an international prospective, observational trial. *Anesth Analg*. 2020;131:1012–1024.
3. Sun Z, Sessler DI, Dalton JE, et al. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. *Anesth Analg*. 2015;121:709–715.
4. Driver CN, Laporta ML, Bergese SD, et al. Frequency and temporal distribution of postoperative respiratory depressive events. *Anesth Analg*. 2021;132:1206–1214.
5. Weingarten TN, Herasevich V, McGlinch MC, et al. Predictors of delayed postoperative respiratory depression assessed from naloxone administration. *Anesth Analg*. 2015;121:422–429.
6. Deljou A, Hedrick SJ, Portner ER, et al. Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. *Br J Anaesth*. 2018;120:798–806.
7. Urman RD, Khanna AK, Bergese SD, et al. Postoperative opioid administration characteristics associated with opioid-induced respiratory depression: results from the PRODIGY trial. *J Clin Anesth*. 2021;70:110167.
8. Chung F, Wong J, Mestek ML, et al. Characterization of respiratory compromise and the potential clinical utility of capnography in the post-anesthesia care unit: a blinded observational trial. *J Clin Monit Comput*. 2020;34:541–551.
9. Gali B, Whalen FX, Schroeder DR, et al. Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. *Anesthesiology*. 2009;110:869–877.
10. Taenzer AH, Pyke JB, McGrath SP. A review of current and emerging approaches to address failure-to-rescue. *Anesthesiology*. 2011;115:421–431.
11. Andersen LW, Kim WY, Chase M, et al. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation*. 2016;98:112–117.