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Respiratory Depression: An Adverse Outcome During Patient Controlled Analgesia Therapy

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Patient-controlled analgesia (PCA) is one of the more popular means of controlling postoperative pain. However, there is very little in the literature concerning the adverse outcome of respiratory depression in PCA. This report is a prospective study of 4,000 patients on PCA postoperatively. Nine of these patients experienced respiratory problems while on PCA. The respiratory depressions were associated with drug interactions, continuous narcotic infusion, nurse- or physician-controlled analgesia and inappropriate use of PCA by patients. This report identified the common precipitating factors in PCA-associated respiratory depression and its prevention.

Keywords: Adverse outcome; postoperative analgesia; respiratory depression

Introduction

Patient-controlled analgesia (PCA) has gained extensive acceptance by patients for its efficacy in controlling pain. PCA allows patients to self-administer small doses of narcotic intravenously when they experience pain, and accommodates for diurnal changes and a wide range of drug requirements among patients. Unintentional or inappropriate triggering of the PCA system produces sedation that subsequently limits further dosing.[1]

PCA provides effective postoperative analgesia,[2,3] less sedation,[2,4] and improved night-time sleep*[,1] compared with conventional parental opioid therapy. Other reported advantages of PCA are improved respiratory function, fewer pulmonary complications, and earlier ambulation and discharge.†[,6,8] The most recognizable advantage is the elimination of unnecessary waiting before the patient receives analgesic.

Although PCA has an excellent safety record, complications have been reported.[7] These problems are related to operator, patient, and mechanical errors. Most of the mishaps that have occurred so far were due either to operator or mechanical error. There is very little in the literature concerning the adverse outcome of respiratory depression in PCA.[8,9] This report describes 9 patients of 4,000 patients who had PCA therapy with adverse outcomes of respiratory depression, associated with drug interaction, continuous infusion, nurse- or physician-controlled analgesia, and inappropriate use. Adverse outcomes of respiratory depression have the potential for disaster, morbidity, and mortality. This report identified the common precipitating factors in PCA respiratory depression and their prevention.

Materials and Methods

From July 1991 to January 1994, the Acute Pain Service (APS) at The Toronto Hospital (Western Division), Toronto, Ontario, Canada, used PCA during the postoperative period for 4,000 patients. The APS team, which con-

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†Finley RJ, Keeri-Szanto M, Boyd D: New analgesic agents and techniques shorten postoperative hospital stay [Abstract]. *Pain* 1984;2: S297.

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sisted of a staff anesthetist and a PCA nurse, visited patients before surgery to explain the use of PCA, and twice daily until PCA was discontinued. PCA pumps (Life-Care PCA Infuser, Abbott Laboratories, No. Chicago, IL) were started in the postanesthesia care unit (PACU) as soon as patients were alert and were continued on the ward. Respiratory rate (RR), level of sedation, and amount of opioid consumed by patients were monitored and documented hourly by nurses on the ward. Adverse outcomes of respiratory depression were prospectively collected by the APS team.

Case Reports (*Table 1*)

Case 1

A 69-year-old woman (81.6 kg, ASA physical status II) with controlled hypertension underwent a right knee arthroplasty for osteoarthritis. She received midazolam 15 mg, alfentanil 1,000 μg at induction, fentanyl 100 μg intraoperatively, and morphine 7 mg intravenously (IV) during her 1.5 hour stay in the PACU. PCA morphine was started at a 2 mg unit dose with a 7 minute lockout time.

The patient was drowsy on arrival in the ward. Six hours after surgery, she was cyanotic and somnolent after receiving 6 mg PCA morphine. Arterial blood gas values at room air were pH 7.2; $PaCO_2$ 69.6 mmHg; PaO_2 25.7 mmHg; bicarbonate 27.1 mmol/L. She received two doses of naloxone 0.2 mg IV. Repeat arterial blood gases values at 40% oxygen (O_2) were pH 7.4; $PaCO_2$ 47.9 mmHg; PaO_2 95.4 mmHg; bicarbonate 24.2 mmol/L. A 12-lead ECG showed pseudonormalization in leads V_2 to V_6. These ischemic changes were thought to be caused by morphine-induced hypoxia. Cardiac enzymes were not elevated and the ECG reverted to preoperative levels.

Case 2

A 12-year-old female (50 kg, ASA physical status I) underwent a 2 hour operation for posterior fusion of congenital vertebrae L_6 to S_2. In the PACU, she received fentanyl 250 μg intraoperatively and morphine 8 mg. The PCA morphine device was set at 1.5 mg unit dose, 7 minute lockout interval, and 4 hour limit of 40 mg.

The patient received two doses of diphenhydramine hydrochloride 25 mg intramuscularly, one at 8:00 PM the evening of the surgery for a presumed allergic reaction to cefazolin sodium and the second at 11:00 AM the next day for pruritis. She slept peacefully one hour later. At 2:45 PM, she was unresponsive and cyanotic. Her respiration was depressed and required manual ventilation with 100% O_2 for 5 minutes. Her RR improved to 20 breaths/min. At 5:00 PM, naloxone 0.4 mg IV was administered because the patient was still drowsy. She had received a mean 8.6 mg/h of morphine. The PCA morphine was decreased from a 1.5 to 1.0 mg unit dose; the lockout period was increased from 7 to 10 minutes; and the 4 hour limit was decreased from 40 to 20 mg. With this PCA setting and specific orders to avoid any sedatives, the patient's pain was controlled without excessive sedation.

Case 3

A 37-year-old woman (70 kg, ASA physical status II) with Von Willebrand's disease, treated hypothyroidism, and ulcerative colitis underwent a right femoral osteotomy. She had previously required a large amount of morphine postoperatively for spinal fusion.

Continuous morphine infusion of 1 mg/h and PCA morphine with a 2.5 mg unit dose, 7 minute lockout period, and 4 hour limit of 40 mg were started because of her narcotic requirement for her last surgery. The PCA morphine dose was increased from 2.5 mg to 3.0 mg on the first day after surgery because of inadequate pain control. On the third postoperative day, the patient was hypotensive, somnolent and disoriented. She had received an average 4 mg/h of morphine and 50 mg of Gravol (dimenhydrinate) intramuscularly every 4 to 6 hours for nausea.

Table 1. Adverse Outcomes of Nine Patients with Respiratory Depression During Patient-controlled Analgesia (PCA)

			Event after surgery		PCA morphine		
Sex	Age (yr)	Procedure	Description	Time (hours)	mg	mg/h	Precipitating factor
Female	69	Knee replacement	Cyanosis, somnolence	6	6.0	2.0	Midazolam 15 mg
Female	12	Lumbar fusion	Cyanosis, unresponsive	24	38.5	8.6	diphenhydramine 25 mg
Female	37	Femoral osteotomy	Somnolence, disoriented	72	48.5	4.0	Gravol 50 mg Bellergal tablet
Male	49	Hip replacement	Somnolence, hypotension	5.5	20.0 PACU 15.0 PCA	6.3	Bolus dose (4 mg)
Male	40	ORIF-tibia	Somnolence, RR 8/min	2.5	20.0 PACU 16.0 PCA	18.4	Bolus dose (20 mg)
Female	14	Thoracolumbar fusion	Cyanosis, unresponsive	72	60.0	7.5	Bolus (13 mg) + continuous infusion
Female	67	Cholecystectomy	Somnolence	13	42.5	3.4	Continuous infusion hypotension
Male	58	Laminectomy	Bradycardia, respiratory depression	3.5	32.5	9.3	PCA overdose
Female	19	ORIF-acetabulum	Somnolence, disoriented	48	35.0	4.4	Inappropriate use

PACU = post anesthetic care unit; ORIF = open reduction and internal fixation; RR = respiratory rate.

Arterial blood gas values at room air were pH 7.5; $PaCO_2$ 39 mmHg; PaO_2 69 mmHg; bicarbonate 29 mmol/L. Naloxone was given without any effect. All narcotics and sedatives were held. It was discovered later that she had taken a Bellergal Spacetab (contains belladonna, ergotamine, phenobarbital). She was given Tylenol #3 (acetaminophen) for her pain without further incident.

Case 4

A 49-year-old man (80 kg, ASA physical status I) underwent a 3 hour general anesthetic for a left total hip replacement. He received diazepam 10 mg premedication and fentanyl 250 μg intraoperatively. During a 2.5 hour stay in PACU, he received morphine 20 mg IV from the nurses, and an additional 7.5 mg through the PCA pump. The PCA device was set at a 1.5 mg unit dose, 10 minute lockout interval, and 4 hour limit of 40 mg.

Three hours after surgery, the PCA unit dose was increased to 2 mg, and a PCA bolus of morphine 4 mg was administered by the anesthesiologist on the ward because of inadequate pain control. The patient had received a total of 35 mg morphine, a mean of 6.3 mg/h. The patient became hypotensive (blood pressure 80/50), diaphoretic and somnolent 2½ hours later. His RR was 10 breaths/min. Supplemental O_2 and naloxone 0.2 mg IV was administered; his RR increased to 16 breaths/min and his blood pressure to 100/76. Oxygen saturation on room air, measured 20 minutes later, was 98%.

The PCA morphine was decreased from a 2 to 1.5 mg unit dose. However, the patient used only 7.5 mg over the next 16 hours. The PCA device was discontinued and oral analgesic was started.

Case 5

A 40-year-old man (75 kg, ASA physical status II) with a history of schizophrenia sustained multiple fractures in an attempted suicide. He underwent repair of a right subtrochanteric, femoral, and tibial plateau fractures. PCA morphine therapy was initiated for postoperative pain control and diazepam (5 mg orally, twice daily) for muscle spasms. PCA morphine was switched to PCA meperidine because the patient complained of auditory hallucination. PCA meperidine was discontinued on the fifth postoperative day without any problem.

Two weeks later, the patient underwent a third general anesthetic for open reduction and internal fixation of the right tibia. He received fentanyl 500 μg for a 2.5 hour operation and morphine 36 mg (20 mg from the nurses and 16 mg from the PCA device in the PACU). He was drowsy but arousable on arrival in the ward. His RR was depressed at 8 breaths/min, and he required prompting to breathe. Naloxone 0.4 mg IV was administered with good effect.

Case 6

A 14-year-old female (55 kg, ASA physical status I) with idiopathic scoliosis underwent a thoracoplasty for spinal instrumentation and fusion of vertebrae T4 to T11. She was comfortable on PCA until the third day after surgery. She had received morphine 102 mg over the previous 48 hours. On the third postoperative day, the APS was called twice because of inadequate pain control. At 9:45 AM, the patient received four boluses of morphine 2 mg IV over 10 minutes from the APS. The 4 hour limit was increased from 40 to 50 mg and the lockout time decreased from 10 to 7 minutes. At 2:10 PM, she received an additional 13 mg morphine IV, and continuous 2 mg/h morphine infusion was started. The PCA bolus dose was increased from 1.5 mg to 3.0 mg without the 4 hour limit. The patient was alert and comfortable at 5:00 PM. By this time, she had received 7.5 mg/h of morphine. Three hours later she was unresponsive and cyanotic with a RR of 4 breaths/min. Naloxone 0.4 mg IV was given, and she promptly recovered consciousness.

The PCA morphine was decreased from 3 to 2.5 mg, the 4 hour limit was reset at 40 mg, and the continuous infusion was discontinued. However the patient was reluctant to use the PCA device, despite frequent encouragement from the nurses. The PCA therapy was discontinued 2 days later and her pain was managed with oral analgesics.

Case 7

A 67-year-old woman (60 kg, ASA physical status II) with atypical myeloproliferative disease, controlled hypothyroidism, and hyperuricemia underwent cholecystectomy. She received meperidine 125 mg during a 2 hour stay in the PACU; a combined therapy of PCA morphine (1.5 mg unit dose, 7 minute lockout interval, 4 hour limit of 30 mg) and continuous infusion (1 mg/h) was initiated for postoperative pain control.

The patient was comfortable with 2.7 mg/h of morphine in the immediate postoperative period. From 12:00 AM to 5:00 AM the next day the patient required more morphine (3.4 mg/h) in addition to the continuous infusion (1 mg/h). At 5:30 AM, she was hypotensive, her blood pressure was 80/50, and she required boluses of normal saline. Four and one half hours later, she became extremely somnolent, her RR was 10 breaths/min, and her pupils were pinpoint. At this point, the total morphine consumption was 42.5 mg. Naloxone 0.3 mg IV was administered with good effect. Her sedation score improved and her RR increased to 16 breaths/min.

Case 8

A 58-year-old man (85 kg, ASA physical status II) with depression and ankylosis spondylitis underwent a C_6 to T_1 laminectomy and fusion for a chronic extradural mass. He received midazolam 2 mg on induction and fentanyl 550 μg for the 6 hour procedure. He was transferred directly from the operating room to the neuro-intensive care unit. PCA morphine (1.5 mg unit dose, 7 minute lockout interval, a 4 hour limit of 40 mg) was started within 30 minutes of his arrival in the unit. He consumed 27.5 mg of morphine between 9:00 to 11:00 PM. At 1:00 AM, he was asleep;

his RR was 12 breaths/min. By this time he had received a total of 32.5 mg of morphine. One half hour later, he was unresponsive, hypotensive (blood pressure 85/50), and bradycardic (heart rate 36 beats/min). Atropine 0.6 mg and naloxone 0.4 mg were administered intravenously with unsatisfactory response. Arterial blood gas values were pH 6.9; $PaCO_2$ 102; and PaO_2 240. The patient required reintubation with a flexible fiberoptic scope. He was ventilated for 6 days after surgery because he developed nosocomial pneumonia. His pain was controlled with 30 to 60 mg codeine intramuscularly without any problems.

Case 9

A 19-year-old female (66 kg, ASA physical status I) underwent a 3 hour general anesthetic for open reduction and internal fixation of a left acetabular fracture. A total of fentanyl 500 μg and alfentanil 2,000 μg was administered intraoperatively.

She received morphine 10 mg IV in the PACU. The PCA morphine was started at a 2 mg unit dose, 7 minute lockout, and 4 hour limit of 50 mg. She was noted to be using the PCA device inappropriately (*i.e.*, pressing the button when she was not experiencing any discomfort). The PCA morphine was decreased from 2 to 1.5 mg unit dose, and the lockout interval increased from 7 to 10 minutes. On the second day after surgery, she was disoriented and somnolent, and her RR was depressed to 10 breaths/min. She had received a total of 35 mg morphine over the previous 7 hours. Naloxone 0.2 mg IV was administered with prompt effect and good recovery of level of consciousness.

Discussion

PCA has gained widespread popularity in Canada and the United States for its use in postoperative pain control. Clinically significant respiratory depression during PCA therapy has been reported to be extremely low. Bennett *et al.*[2] reported no respiratory depression in more than 1,300 recordings of RRs. McKenzie *et al.*,[10] in their experience of more than 18,000 patients, reported no clinical overdose with PCA morphine set at a 1 mg unit dose or PCA meperidine set at a 10 mg unit dose and a 6 minute lockout interval. However, Etches[8] reported an incidence of 0.5%, which is comparable to our series of 0.33%, or 9 of 4,000 patients. Respiratory depression associated with intramuscular opioid and epidural morphine is 0.9%.[11,12] Increasing awareness and understanding of the precipitating factors of respiratory depression in patients using PCA will further reduce the incidence.

White[7] categorized potential problems into (1) operator errors, (2) mechanical problems or malfunctions, and (3) patient errors, such as failure to understand the use of PCA or intentional analgesia abuse. Reported mechanical errors or malfunctions were overdoses from a cracked prefilled syringe,[13] defective one-way valve,[7] electrical corruption of the PCA pump's program,[14] and death caused by accidental massive overdose of meperidine.[15] Documented operator errors include misprogramming the PCA device,[7] improper loading of the syringe or cartridge,[16] and failure to cross-clamp the tubing connecting the cartridge to the intravenous catheter resulting in opioid overdose.[7] Patients' errors were primarily due to inadequate education or comprehension of the function of the PCA device, which has resulted in oversedation and respiratory depression when the PCA push button was mistakenly pushed instead of the nurse call button,[17] or when the PCA button was pushed at the illumination of green light on the PCA machine.[18] In our study, however, we did not document any of these potential problems. Instead, we found that PCA-induced somnolence and respiratory depression were associated with drug interaction, continuous narcotic infusion, nurse- or physician-controlled analgesia, and inappropriate PCA use.

Adverse outcome of respiratory depression can be due to drug interactions among PCA and other medications prescribed for patients. Drug interaction occurred in three cases in which midazolam, Gravol, diphenhydramine, and Bellergal were implicated. The sedative effects of these drugs can potentially cause excessive sedation and somnolence, as in the case of our 69-year-old female patient (Case 1) who received narcotics (fentanyl 100 μg and alfentanil 1,000 μg) and midazolam 15 mg and had respiratory depression 6 hours after surgery. Although the elimination half-life of midazolam is 1 to 4 hours, 8% of patients may have prolonged elimination half-life of midazolam because of defective hepatic metabolism[17,18]; these patients may have longer periods of drowsiness and be more prone to interaction with PCA morphine. In Cases 2 and 3, PCA-induced respiratory depression and somnolence were associated with concomitant administration of Benadryl, Gravol, and Bellergal. Respiratory complications related to drug interaction with lorazepam, perphenazine, doxapram, and other narcotics that patients received perioperatively have also been reported.[8,9,21] Therefore, sedatives and antiemetics should be used sparingly; these are not appropriate for all patients on PCA. If sedatives or antiemetics are required, extra vigilance and precaution are strongly recommended.

Adverse outcome of respiratory depression in PCA patients may be caused by continuous infusion or additional boluses given by physicians or nurses. Dosage escalation to meet the patients' analgesic demand because of increased narcotic dose delivered by PCA or continuous or additional boluses given by nurses or physicians resulted in five cases of primary opioid overdose in our series. Two of our patients were on continuous opioid infusion (Cases 6 and 7). The continuous mode of opioid delivery was initially introduced to provide a more stable level of analgesia and thus better sleep patterns with less interruption because of episodic pain. Two recent studies[22,23] suggest that this theoretical benefit has not been proven. When compared with PCA on demand mode alone, the patients who were on the combined mode consumed significantly more analgesic but their pain relief was not superior. In contrast to on-demand PCA therapy, the use of continuous infusion obligates the patient to receive a minimum dose of nar-

cotic. The consequences of a mistake in continuous infusion are potentially more serious because the narcotic is administered without the patient having to activate the PCA device.[24]

Fleming and Coombs[9] reported eight cases of complications (respiratory depression, seizure, hallucination) associated with PCA use in 1,122 patients: the majority of the complications (5 of 8) occurred in patients who were on the combined mode, continuous and demand PCA. In our study, opioid overdose (Case 6) occurred in a 14-year-old female who received escalating doses of morphine from the APS, morphine infusion (2 mg/h), and PCA morphine (3-mg unit dose) without a 4 hour limit. Severe respiratory depression caused by PCA morphine overdose resulted in reintubation in a patient 3.5 hours after surgery (Case 8). In Case 7, hypotension preceded somnolence in a 67-year-old woman who was on a combined-mode PCA therapy. There are recent reports that hypovolemia or shock states can lead to decompensation and respiratory depression in patients who previously tolerated PCA narcotic dose.[25,26] This is believed to be caused by an imbalance of central chemoreceptor occupancy and reticular formation potential.

Persons giving supplemental doses of analgesic to patients on PCA may precipitate respiratory depression. In our series, two patients (Cases 4 and 5) received boluses of morphine from nurses or physicians. Similar instances involving a spouse administering opioid via the PCA pump have been reported.[9,27] Our patients received two routes of opioids, thus bypassing the inherent safety feature of PCA (*i.e.*, that the patient cannot self-administer additional opioid if she or he is too sedated). In our hospital, the problems with excessive sedation and respiratory depression were recognized and corrected through the education of the nurses and other health care providers, and by close monitoring of patients who received boluses of opioid from persons other than the patients themselves.

In addition, inappropriate use of the PCA device can cause respiratory depression. The adverse outcome of respiratory depression caused by inappropriate use of the PCA device occurred in a young girl despite preoperative education before PCA therapy. Stevens *et al.*[28] reported a case of PCA-induced oversedation attributed to the inappropriate use of or tampering with the PCA device by a patient who had a history of drug abuse; they concluded that these patients should be excluded from PCA use. However, we have given PCA without problems to drug addicts in our institution. Patient selection is important to the successful use of PCA.

Among the reasons some patients are more susceptible to the respiratory effects of narcotics while on PCA is patient's variability in requirement for analgesia. Several studies[1,10,24] have shown that analgesic requirements among patients and the resultant therapeutic concentrations are highly variable. There may be four- to sixfold differences in opioid requirements, independent of patients' age and weight. Morphine requirements during the first three postoperative days varied from 0 to 16.5 mg/h, but the median requirement was 1.1 to 2.6 mg/h.[3]

Other complications associated with the use of PCA include hypotension, hallucination, and myocardial ischemia. Airway obstruction in patients with abnormal airways and sleep apnea,[8,21,29] acute pancreatitis caused by spasm of the sphincter of Oddi,[30] and delayed diagnosis of pulmonary emboli[31] are among the problems reported in patients on PCA.

PCA is becoming more popular as a mode of managing postoperative pain. Although its efficacies and benefits are indisputable, there are occasional problems associated with the use of PCA. In our series, four patients were cyanotic: one required reintubation, and the others had ECG changes of myocardial ischemia. Fortunately, there were no myocardial infarctions or deaths.

We no longer use the combined mode: continuous infusion and PCA mode. Anesthesiologists and PCA nurses have been advised of the problem of co-administering intravenous and PCA opioids. Nurses are taught that drug interaction with PCA may cause respiratory depression. The adverse outcome of respiratory depression has potential for disaster. Increasing awareness and education about precipitating factors can further reduce the incidence of PCA respiratory depression. When RR and sedation level are monitored hourly, PCA is a safe method of administering postoperative analgesic.

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