

Respiratory depression associated with patient-controlled analgesia: a review of eight cases

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Patient-controlled iv delivery of opioids for postoperative pain management is a popular alternative to the traditional im route of administration. However, occasional patients receiving opioids in this manner develop severe respiratory depression. The purpose of this paper is to determine the incidence of, and factors contributing to, the development of this complication. To do this, the Office of Medical Quality Improvement retrospectively searched for reports of respiratory depression in a database compiled from the charts of approximately 1600 patients who had received PCA at the University of Alberta Hospitals in 1992. Eight cases of serious respiratory depression were detected. Factors associated with the occurrence of respiratory depression included the concurrent use of a background infusion, advanced age, concomitant administration of sedative/hypnotic medications, and pre-existing sleep apnoea syndrome. No cases were attributed to operator error or equipment malfunction. In conclusion, the risk of respiratory depression with patient-controlled opioid administration is similar to that observed when opioids are delivered by the traditional im or spinal routes. The safe and effective use of patient-controlled analgesia depends upon knowledgeable medical and nursing staff, clearly defined nursing policy and procedures, and frequent patient follow-up.

L'administration contrôlée par le patient (PCA) de morphiniques iv pour le traitement de la douleur postopératoire est une alternative valable à la voie im traditionnelle. Cependant, à l'occasion, des malades sous morphiniques administrés de cette façon souffrent de dépression respiratoire grave. Cette étude vise à déterminer son incidence et les facteurs qui contribuent à

l'apparition de cette complication. Avec cet objectif en vue, le bureau médical de l'amélioration de la qualité a recherché rétrospectivement les cas de dépression respiratoire dans une banque de données compilées à partir des dossiers de 1600 patients traités par PCA dans les hôpitaux de l'université de l'Alberta en 1992. On a retracé huit cas de dépression respiratoire grave. Les facteurs associés avec la survenue de cette dépression comprenaient l'administration concomitante d'une perfusion continue ou de sédatifs, la vieillesse et la pré-existence du syndrome d'apnée du sommeil. Des erreurs humaines ou instrumentales n'ont jamais été mises en cause. Pour conclure, le risque d'une dépression respiratoire avec la PCA morphinique est le même que celui qu'on retrouve avec les morphiniques im ou rachidiens. La sécurité et l'efficacité de l'analgésie auto-contrôlée dépend d'un personnel soignant et médical avisé, de politiques et protocoles bien établis et d'une surveillance étroite.

The use of patient-controlled analgesia (PCA) for the management of postoperative pain has grown rapidly. Patient-controlled analgesia is often presented as an effective alternative to traditional *im* opioids without the complexity of and concern for respiratory depression associated with epidural opioid administration. Few would argue against the effectiveness of PCA, but there is little evidence to support an argument that the risk of severe respiratory depression is less than with epidural opioids. In fact, the limited data suggest that the incidence may be greater with PCA than with epidural opioid administration.¹⁻⁴

This paper reviews eight cases of severe respiratory depression occurring in patients receiving PCA at the University of Alberta Hospitals.

Methods

Description of the acute pain management service

The University of Alberta Hospitals has an established acute pain management service (APMS) which cares for approximately 2500 patients annually. Most are adults undergoing major orthopaedic or general surgical procedures, and approximately 80% receive PCA postopera-

Key words

PAIN: postoperative;
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tively. The APMS is staffed by a dedicated staff anaesthetist who provides the service on a weekly basis and is on 24 hr call during that week. This individual sees patients preoperatively and daily (including weekends and holidays) following surgery until the patients no longer require parenteral analgesics. At night, calls are initially taken by the anaesthesia residents; if the resident wishes, he/she may contact the staff anaesthetist. With the exception of a single intensive care unit, PCA is prescribed and managed by the anaesthesia staff and residents only. The hospital employs a nurse specialist who oversees nursing in-service education and development of the necessary nursing policy and procedures associated with PCA. The hospital uses preprinted PCA order sheets. Opioids for PCA are supplied in two standard preparations, morphine $2 \text{ mg} \cdot \text{ml}^{-1}$ and meperidine $20 \text{ mg} \cdot \text{ml}^{-1}$. The dose and lockout interval are left to the discretion of the anaesthetist. Background infusions are used in a small minority of patients. The Graseby PCAS patient-controlled infusion device is used throughout the hospital.

Data collection

This paper reviews all cases of severe respiratory depression in adult orthopaedic and general surgical patients receiving PCA from January, 1992 until March, 1993. This was accomplished with the support of the Office of Medical Quality Improvement (MQI). The charts of all adult orthopaedic and general surgical patients are reviewed by MQI at the time of admission, 72 hr after admission, and within two weeks following discharge. All adverse patient occurrences are noted and entered into the MQI database. Such occurrences are deemed to have occurred if they appear anywhere in the patient's chart, including the nursing notes, physicians' notes, or other consultations. The Office of Medical Quality Improvement does not attempt to determine the validity or severity of the occurrence; nor is there any assignment of responsibility. Adverse occurrences are brought to the attention of the relevant departmental representatives who analyze the events in detail.

For this paper, MQI searched a database compiled from the charts of approximately 1600 patients. The search criteria were respiratory depression associated with anaesthesia. (All PCA on the orthopaedic and general surgical wards is prescribed and monitored by an anaesthetist.) Charts for these patients were reviewed by the author. It should be noted that this search strategy may overlook patients in whom PCA was temporarily discontinued or changed because of sedation or respiratory depression which the nurse or physician felt was important but not immediately dangerous.

Results

The Office of Medical Quality Improvement detected eight patients meeting the defined criteria. Three additional patients, not in the MQI database, were brought to the attention of the author by the surgical staff. All 11 patients had a diagnosis of opioid-induced respiratory depression, all were receiving PCA morphine, and all received at least one dose of naloxone. Following a review of the charts, three patients were excluded from further discussion because the severe respiratory events occurred early in the postoperative period, before the patients had received any opioids via the PCA device. Relevant data for the remaining eight patients are summarized in the Table. All patients recovered uneventfully. To date, we are not aware of any deaths or long-term adverse sequelae attributable to the use of PCA in our institution.

Case reports

Case #1

A 52-yr-old man in general good health underwent an uneventful total hip arthroplasty. During the procedure the patient received morphine 9.5 mg and fentanyl 200 μg . Patient-controlled analgesia with morphine was started in the post-anaesthetic recovery room (PARR) with a background infusion of $1 \text{ mg} \cdot \text{hr}^{-1}$ and a bolus dose of 1 mg. Approximately two hours after the initiation of PCA the patient was found on the ward unresponsive with a respiratory rate of four breaths per minute. The patient had received approximately 7 mg, PCA morphine. The patient was treated with oxygen by mask and naloxone 0.8 mg *iv* and recovered immediately. He was subsequently managed with *im* morphine.

Case #2

A 42-yr-old man in general good health underwent an uneventful appendectomy and subsequently received PCA morphine (2 mg bolus and a $1 \text{ mg} \cdot \text{hr}^{-1}$ background infusion). Over the next 28 hr the patient received approximately 61 mg morphine, of which 28 mg were delivered by a background infusion. Twenty-four hours after surgery the patient was noted to be confused and drowsy. Pulse oximetry revealed a SpO_2 of 59%. The background infusion was discontinued and the patient received oxygen by nasal prongs. Two hours later the patient was confused with a SpO_2 of 68% despite the administration of oxygen by nasal prongs. Respiration was charted as shallow with a respiratory rate of 32 breaths/ min^{-1} . Arterial blood gas analysis revealed PaO_2 46 mmHg, PaCO_2 55 mmHg, and $[\text{H}^+]$ $55 \text{ nmol} \cdot \text{L}^{-1}$ (pH 7.25). The patient was treated with naloxone 0.4 mg *iv* and recovered uneventfully. Patient-controlled analge-

TABLE Respiratory depression with PCA

Case #	Age	Sex	Procedure	Pre-existing medical factors	PCA Morphine			Other Medications	Presentation	Treatment
					Bolus (mg)	Lock-out (min)	Back-ground (mg · hr ⁻¹)			
1	52	M	Total hip replacement	None	1	10	1	None	Unroutable one hour after returning from OR. Approximately 7 mg PCA morphine delivered RR of 4.	Oxygen, naloxone 0.8 mg <i>iv</i> .
2	42	M	Appendectomy	None	2	10	1	None	Confused and drowsy SpO ₂ 59% 24 hr postop. Treated with oxygen and background stopped. SpO ₂ 68% with oxygen two hours later. ABG's PaO ₂ 46, PaCO ₂ 55, H ⁺ 55.	Oxygen, naloxone 0.4 mg <i>iv</i> .
3	64	F	Total knee replacement	None	1.4	10	1	Indomethacin	11.8 mg PCA morphine during first four hours postop. RR of 4, 6 hours postop. Very drowsy.	Oxygen, naloxone 0.1 mg <i>im</i> . Increased RR to 6-7. Easily rousable. Bolus decreased to 1 mg and background stopped.
4	84	F	Hysterectomy BSO, omentectomy	Age	0.6	10	None	None	PCA morphine in 6 mg in 2 hr following return from OR. RR of 4. Difficult to rouse.	Oxygen, naloxone 0.4 mg <i>iv</i> .
5	85	F	Colostomy	Age	1	10	None	None	Morphine 15 mg <i>iv</i> in OR and PARR. PCA morphine 6 mg in first two hours after returning from PARR. Found drowsy with a RR of 7.	Oxygen, CPAP, naloxone 0.4 mg <i>iv</i> .
6	27	M	Facial fracture awaiting surgery	None	2	8	None	Lorazepam 1 mg s.l. at 2400 hr	Stable until 2400 hr. PCA morphine 8-10 mg q4h. No PCA use after 2400 hr. Found obstructed and cyanotic.	Oxygen, CPAP, naloxone 0.4 mg <i>iv</i> .
7	56	M	Bilat. total knee replacement	Probable sleep apnoea. Not diagnosed preoperatively	1	10	None	None	Required nasal airway postop. Very sedated. Narcan 0.1 <i>iv</i> given and bolus decreased to 0.6 mg. Bolus increased to 1.0 mg at 0700 on following morning. Found at 1130 not rousable. ABG's PaO ₂ 76, PaCO ₂ 60, H ⁺ 53.	Oxygen, naloxone 0.4 mg <i>iv</i> . PCA stopped. Switched to Ketorolac <i>im</i> .
8	27	M	Donor nephrectomy	None	2	8	None	None	Found cyanotic with shallow respirations 24 hr postop. PCA morphine 20-30 mg q4h for 24 hr.	Oxygen, naloxone 0.4 mg <i>iv</i> 2 doses. PCA held. Bolus decreased to 1 mg and lockout increased to 12 min.

sia was discontinued and the patient required no further analgesics for 48 hr.

Case #3

A 64-yr-old woman in general good health underwent a total knee replacement under general anaesthesia. During surgery and in the PARR the patient received fentanyl 75 μg and morphine 21 mg *iv*. Patient-controlled analgesia with morphine was ordered with a bolus dose of 1.4 mg and a background infusion of 1 mg \cdot hr⁻¹ which was started in the PARR. In addition, the patient received indomethacin 100 mg *pr* in the PARR. Five hours later the PCA was discontinued because of excessive sedation and a respiratory rate of 6–8 breaths \cdot min⁻¹. Over the previous four hours the patient had received 11.8 mg morphine via the PCA device, including approximately 5 mg in the background infusion. Two hours later the patient was very drowsy and the respiratory rate had decreased to 4–5 breaths \cdot min⁻¹. The patient received naloxone 0.1 mg *im* and the respiratory rate and level of consciousness improved considerably. Patient-controlled analgesia was restarted the following morning with a bolus of 1 mg and no background infusion. The patient required morphine 2–3 mg every four hours to obtain satisfactory analgesia. No further problems were noted.

Cases #4 and 5

Both patients were elderly women (aged 84 and 85 yr) who underwent laparotomies. Patient #4 received morphine 19.5 mg perioperatively before PCA, and an additional 6 mg via PCA following her return to the ward. Patient #5, who weighed 46 kg, received morphine 15 mg perioperatively plus 6 mg via PCA. Both patients were found to be very sedated and bradypnoeic (4–7 breaths \cdot min⁻¹) within two hours of returning to the ward. Both responded immediately to treatment with oxygen and intravenous naloxone. It should be noted that the relatively large doses of morphine administered perioperatively to both of these patients may have been partly responsible for the severe respiratory depression seen a short time later on the ward.

Case #6

An otherwise healthy 27-yr-old man was admitted with a facial smash as a result of being kicked by a bull while participating in a rodeo. His medical history was unremarkable and he was taking no medications. There was no evidence of airway or cardiorespiratory compromise. His level of consciousness was normal and there was no suggestion of an intracranial injury. Before surgery he was ordered PCA morphine with a bolus of 2 mg, a lockout interval of eight minutes, and no background infusion.

During the day the patient was alert and stable. His morphine consumption was 8 to 10 mg q4hr. At midnight the patient received lorazepam 1 mg *po*. From 0000 to 0320 hr the patient received only 2 mg of PCA morphine. At 0320 hr the patient was found, during routine rounds, to be cyanotic with severe inspiratory obstruction, and a Glasgow coma score of 3. He was promptly resuscitated with oxygen, an oropharyngeal airway, and CPAP. With this his SpO₂ returned to normal immediately, but he did not regain consciousness. He then received naloxone 0.4 mg *iv* and regained consciousness promptly. The patient made a full and immediate recovery. Patient-controlled analgesia was discontinued, and *im* codeine ordered in its place. The following night, the patient received codeine 60 mg *im* plus lorazepam 1 mg, and again, the nurses noted that he was very sedated and partially obstructed whenever his head fell forward. With these episodes his recorded SpO₂ decreased as low as 60%. He was managed with close observation. The lorazepam was subsequently omitted. No further problems occurred.

Case #7

A 56-yr-old man underwent bilateral total knee replacement under general anaesthesia. Postoperatively the patient was very sedated and required a nasal airway to maintain airway patency. Despite modest doses of morphine (16 mg over 12 hr) via PCA, the patient became very sedated and hypercapnic. On the morning of the first postoperative day the patient complained of pain unrelieved by bolus doses of morphine 0.6 mg. The bolus dose was increased to 1 mg, and four hours later the patient was found to be unrousable with inspiratory obstruction. Arterial blood gas analysis revealed PaO₂ 76 mmHg, PaCO₂ 60 mmHg, and [H⁺] 53 nmol \cdot L⁻¹ (pH 7.27). On reviewing the patient's history, both before and during admission, it was concluded that the patient suffered from sleep apnoea syndrome. Patient-controlled analgesia was discontinued and the patient subsequently received *im* ketorolac for analgesia.

Case #8

A healthy 27-yr-old man underwent an uneventful donor nephrectomy. Postoperatively, PCA morphine was initiated with a bolus dose of 2 mg, a lockout interval of eight minutes, and no background infusion. No other sedatives or opioids were administered. Over the first 24 hr postoperatively, the patient self-administered an average of 20–30 mg morphine every four hours. Approximately 24 hr postoperatively the patient was found to be cyanotic with shallow respirations. He was treated with oxygen and naloxone 0.8 mg *iv* with immediate recovery. Patient-controlled analgesia was withheld until the patient requested additional analgesia. The PCA bolus dose was

decreased to 1 mg and the lockout interval increased to 12 min. Subsequent PCA requirements were minimal – 0–2 mg every four hours.

Discussion

In the population studied, the incidence of reported, severe respiratory depression associated with PCA was 0.5%. This is less than that reported for *im* opioids (0.9%),⁵ but more than for intrathecal (0.36%) and epidural opioids (0.09–0.2%).^{3,4} These findings are in agreement with those of Fleming and Coombs¹ who reported five cases of severe respiratory depression in 1122 postoperative patients receiving PCA and with those of MacIntyre *et al.* who found four cases among the 747 patients reviewed.²

The true incidence of respiratory compromise associated with postoperative opioid analgesia, regardless of the route of administration, may be higher than reported for two reasons. Firstly, studies that address this issue are based on retrospective chart reviews. There may be instances of sedation and/or presumed respiratory depression which are deemed to be severe but not dangerous by the physician or nurse; these may result in a change of therapy without mention of respiratory depression. Secondly, respiratory depression is usually defined as excessive sedation and/or bradypnoea. This definition does not consider the poor correlation between respiratory rate and PaCO₂,⁶ or the potentially serious problem of postoperative hypoxaemia. This problem is illustrated by Catley *et al.*⁷ who found that ten of 16 postoperative patients receiving *iv* morphine infusions experienced multiple episodes of hypoxaemia (defined as SaO₂ < 80%), not associated with bradypnoea. In addition, all episodes of hypoxaemia occurred during sleep, an obvious problem if sedation is part of the definition. Despite these problems in determining the true incidence of severe respiratory depression, the data suggest that PCA provided in the milieu of a comprehensive pain management service compares favourably with both traditional *im* and spinal opioids.

There are several factors contributing to the development of respiratory depression with PCA. Early reports^{8–11} focused attention on operator errors such as misprogramming, and mechanical problems or malfunctions which led to overdoses of opioid. Recent studies^{1,12} have found that such serious errors are very uncommon. Pharmacokinetic factors including hypovolaemia¹³ and acute renal failure¹⁴ have also been cited. Hypovolaemia may result in higher initial serum concentrations and a slower early distribution phase, both of which will result in greater CNS concentrations of the drug. If hypovolaemia is associated with hypotension and hypoxaemia, CNS hypoxia may potentiate any opioid-induced respiratory de-

pression. Prolonged hypovolaemia may decrease drug clearance. Administration of morphine or meperidine to patients with renal insufficiency may lead to the accumulation of active metabolites.

In this review problems included the concurrent use of background infusions (cases #1–3), extremes of age (cases #4 and 5), concomitant administration of additional sedative/hypnotics (case #6), preexisting respiratory compromise (case #7), and excessively liberal prescribing (case #8).

Background infusions

The use of a background infusion with PCA is associated with a higher incidence of severe respiratory depression than is PCA alone.^{1,12} Although less than 10% of patients in the present study received a background infusion, 38% of the eight cases reported are in this group (see Table). Fleming and Coombs¹ reported that three of five patients who developed severe respiratory depression and two of three patients who developed other major complications received background infusions, even though they were used in only 7% of the 1122 patients reviewed. Notcutt and Morgan¹² cite a 2.5% incidence of respiratory complications in patients receiving background infusions, compared to 1% in those with PCA only.

Most studies fail to demonstrate any benefits when PCA is combined with a background infusion.^{15–18} Indeed, several studies have shown that opioid requirements are increased.^{15–17,19} Parker *et al.*¹⁸ found that three of 78 patients receiving a background infusion of morphine had prolonged episodes of postoperative hypoxaemia when monitored with continuous pulse oximetry, compared with no episodes of hypoxia in patients receiving PCA alone. Even those who advocate the use of background infusions do so cautiously, recommending low hourly infusion rates or a lower hourly limit to PCA.^{20,21} Patients for whom background infusions may be indicated include patients with a preexisting or demonstrated opioid tolerance.

PCA in the elderly

The safe and effective use of PCA by the elderly is often difficult. Pharmacodynamic and pharmacokinetic changes are in part responsible.²² Elderly patients are more susceptible to a given serum concentration of opioid and sedative medications.²² In addition, a lower initial volume of distribution and reduced protein binding may potentiate the effect of an initial bolus dose. Clearance of drugs by the kidney and liver is reduced, and the volume of distribution of lipophilic drugs may increase with age because of an increased percentage of body fat; the result is an increased elimination half-life. The greatest impediment to the use of PCA by the elderly is the in-

