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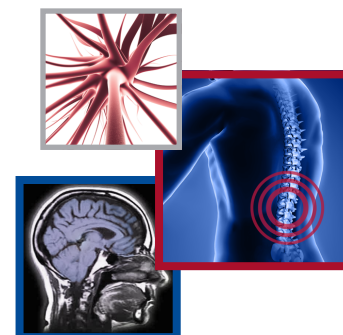
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Opioid-induced respiratory depression in the acute care setting: a compendium of case reports

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Practice points

- Opioid-induced respiratory depression (OIRD) is a potentially fatal complication of opioid use both in clinical (perioperative and acute/chronic pain relief) and nonclinical settings (misuse/abuse).
- Since 1980, 105 case reports on critical OIRD in the acute care setting were published in the literature as retrieved from PubMed.
- The majority of patients had no underlying comorbidities that placed them at increased risk for OIRD. Only 30–40% of cases had a comorbidity possibly related to the OIRD including sleep-disordered breathing, renal impairment, obesity and pulmonary disease, neurological disorders and polymorphisms of the CYP450 enzyme system.
- Most frequently reported opioid related to respiratory depression was morphine, followed by sufentanil and fentanyl. Neuraxial administration was the most frequent route associated with OIRD followed by intravenous dosing.
- In case reports since 2000, complications in women were disproportionately more common, consistent with their higher opioid sensitivity. Advanced age was not a factor related to OIRD.
- This analysis of case reports indicates that OIRD is a significant cause of preventable morbidity and mortality and that OIRD is difficult to predict. Dose titration to effect alongside comprehensive and frequent respiratory and level of consciousness monitoring remains the most important safeguard against preventable harm to undetected OIRD.

SUMMARY Opioid-induced respiratory depression (OIRD) is a potentially fatal complication of treatment with opioids. Little is known about patient- and case-related factors associated with OIRD. One-hundred-and-five available case reports on OIRD in 134 patients (12 years and older) in the perioperative, obstetric or emergency care setting, published since 1980, were retrieved from the literature. The most frequently reported case-related factors were: morphine use, perioperative setting and obstetrics, neuraxial or intravenous administration. The most frequently reported patient-related factors involved were: female gender, sleep-disordered breathing, obesity, renal impairment, pulmonary disease and CYP450 enzyme polymorphisms. While the analysis has limitations, it confirms that OIRD in the acute setting involves complex and interrelated factors and is a significant cause of preventable morbidity and mortality.

KEYWORDS

• analgesia • case report
• case series • mortality
• opioid-induced respiratory depression • opioids
• perioperative complications • respiratory depression

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Opioid-induced respiratory depression (OIRD) is a potentially fatal complication of opioid use in both acute and chronic pain therapy, and nonclinical settings, such as opioid misuse and addiction [1]. Although fatalities from OIRD in the clinical setting are well described in case reports, there is no compendium of patient and nonpatient-related factors that are common to these serious adverse events. We have previously published an analysis of case reports of OIRD in pediatric patients (0–12 years of age) and patients treated with opioids for chronic pain [2,3]. In the current study, we apply our methodology from earlier publications to the cohort of case reports describing OIRD in adolescent and adult patients with OIRD in acute care settings. Our prior analysis of OIRD case reports in pediatric patients revealed that fatal OIRD was associated with children receiving codeine following tonsillectomy or adenoidectomy. Our publication coincided with a US FDA black box warning of codeine use in these procedures, prompted in part by ten deaths and three reported overdoses associated with codeine in the period 1969–2012 [4]. This association strengthened our suspicion that a careful analysis of case reports may reveal specific demographic, pharmacological or clinical covariates that confer additional risk for OIRD. We describe our findings for patients receiving opioids for acute pain, including obstetrical pain, and patients prescribed opiate-containing formulations for cough and dyspnea.

Methods

We retrieved case reports and case series on OIRD from the PubMed database written in English, Dutch or French during the period 1980–2013 [5]. Included were cases of patients 12 years or older who developed OIRD in response to opioids during treatment of pain in the perioperative setting or emergency department, labor pain, cough/dyspnea or procedural sedation. Cases related to human errors involving errors in prescribing or in the programming of infusion devices were excluded.

OIRD was defined as a clinical assessment of impaired spontaneous ventilation requiring one of the following interventions: Mask ventilation; effective reversal of OIRD with naloxone and/or doxapram; endo-tracheal intubation; positive pressure ventilation followed by unplanned admission to an intensive care or monitored setting.

Causality between opioid treatment and OIRD was established by authors AD and MN, and differences in opinion were resolved by consensus. *A priori*, the cases were divided into those published between 1980 and 1999, and those between 2000 and 2013, since this chronological partition was meaningful in our study of OIRD in chronic pain, as well as divided into three age groups, namely 12–30, 31–60 and 61 years of age or older. The following variables were retrieved from each case: gender, age, comorbidities, opioid, route of administration, clinical setting and outcome.

Results

• Literature

The PubMed search resulted in 4798 publications of which 4693 did not meet inclusion criteria or cited adverse events not deemed causally related to opioids by the authors. In total, 105 case reports were included in our analysis: 70 reports involving 97 patients during 1980–1999 [6–75], and 35 involving 37 patients during 2000–2013 [76–110]. The number of reports per year decreased from 4.9 cases per year in 1980–1999 to 2.9 cases per year in 2000–2013.

• Patient characteristics

Patient age was not significantly different before or after 2000 (Table 1). Men and women were equally represented prior to 2000 but women outnumbered men 2:1 after 2000. The majority of patients had no underlying medical or neurological disease that predisposed them to OIRD. Only 31% of patients prior to 2000 and 43% of patients since the year 2000 had comorbidity possibly related to the OIRD. These predispositions included sleep-disordered breathing (SDB), renal impairment, obesity (BMI >30) and pulmonary disease prior to 2000, whereas since 2000 comorbidities predisposing to OIRD included renal impairment, pulmonary disease, neurological disorders and polymorphisms of the CYP450 enzyme system (Table 1). The latter occurred especially in cases in which metabolites produce active compounds (such as in the case of tramadol and codeine).

• Case-related specifics

Morphine was the preeminent opioid used in both pre- and post-2000 periods (>30%) whereas sufentanil and fentanyl were the next most common in the pre- and post-2000 time periods (Table 2). Alfentanil was only

Table 1. Characteristics of all 134 patients described in 105 case reports on critical opioid-induced respiratory depression in the acute care setting.

Patient characteristics	Period (year)	
	1980–1999	2000–2013
Number of cases	97	37
Gender:		
– Men, n (%)	46 (47)	14 (38)
– Women, n (%)	50 (52)	21 (58)
– Unknown, n	1	2
Age:		
– Median (range), years	51.5 (16–85)	44.0 (14–81)
– Cohort 12–30 years, n (%)	23 (24)	14 (38)
– Cohort 31–60 years, n (%)	36 (37)	9 (24)
– Cohort 61 years and older, n (%)	37 (38)	12 (32)
Underlying disease:		
– Sleep-disordered breathing, n (%)	16 (17)	1 (3)
– Renal impairment, n (%)	9 (9)	3 (8)
– Obesity, n (%)	4 (3)	2 (6)
– Pulmonary disease, n (%)	2 (2)	1 (3)
– Neurological disorders, n (%) [†]	–	5 (14)
– CYP450 polymorphisms, n (%)	–	5 (14)

[†]Includes poliomyelitis, myopathy, encephalopathy, M. Parkinson, Angelman syndrome.

incriminated in OIRD prior to the year 2000. Conversely, remifentanyl was incriminated in six cases, three of which involved Patient-controlled analgesia (PCA) for labor pain, all since the year 2000. Tramadol was reported as cause of OIRD in seven cases (six after 2000). The setting in which OIRD was most frequently reported was perioperative (with 86 and 69% of cases in pre- and post-2000 periods, respectively), followed by the obstetrical ward. In both periods, neuraxial was the most common route of administration followed by the intravenous route, both nurse administered and PCA.

• Outcomes

Serious adverse events resulting in hypoxic brain damage or death were reported in six (9%) patients and two (6%) patients in pre- and post-2000 cases, respectively.

Discussion

• Opioid-induced respiratory depression

In this study, we included reports on 134 patients that developed OIRD in an acute setting. Opioids have a direct depressant effect on neurons that express the MOP (μ -opioid peptide) receptor in the respiratory centers of the brainstem [111]. Respiratory depression is life threatening when depression of respiratory neurons exceeds the respiratory stimulatory effects of retained CO_2 or other stimulants,

such as pain, heightened arousal and visual cues. At low opioid dosages or slow infusion rates, the patient will continue breathing but arterial P_aCO_2 (PaCO_2) will increase (hypercapnia). The accumulating P_aCO_2 stimulates breathing via activation of central and peripheral chemoreceptors. When an opioid dose becomes a threat to the patient's safety, breathing activity will decrease further and become irregular and apneic even at high arterial P_aCO_2 [112]. While physicians may have some sense of 'standard' dosing regimens, opioid sensitivity is highly variable among patients (dose may vary by a factor of 40), and care is always required when dosing a patient in any acute setting. In one of the retrieved case reports, Lötsch *et al.* describe a young female that received morphine for postoperative pain relief. Due to the slow onset times of morphine (related to the lag time needed to cross the blood–brain barrier), the patient's pain was not alleviated immediately and further infusions of morphine were given eventually leading to a fatal cardiac arrest [93]. This was a classic example of the greater potency but slower time to onset of opioid analgesia in women compared with men as described by Sarton *et al.* [113], a pharmacokinetic/pharmacodynamic nuance, unbeknown to most physicians. In most cases reports, OIRD developed without any indication of an obvious overdose, suggesting that OIRD may

Table 2. Case-related specifics.

Case characteristics	Period (year)	
	1980–1999	2000–2013
Number of cases	97	37
Drugs involved:		
– Morphine, n (%)	32 (33)	15 (41)
– Sufentanil, n (%)	26 (27)	3 (8)
– Fentanyl, n (%)	15 (15)	7 (19)
– Alfentanil, n (%)	12 (11)	–
– Remifentanyl, n (%)	–	6 (16)
– Codeine, n (%)	2 (2)	3 (8)
– Tramadol, n (%)	1 (1)	6 (16)
Setting:		
– Perioperative (nonobstetric), n (%)	84 (86)	26 (70)
– Obstetrics, n (%)	10 (11)	6 (16)
– Acute pain, n (%)	2 (2)	3 (8)
– Sedation, n (%)	1 (1)	–
– Cough/dyspnea, n (%)	–	1 (3)
Administration route:		
– Neuraxial, n (%)	43 (44)	12 (32)
– Intravenous, n (%) [†]	37 (38)	15 (41)
– Intravenous PCA, n (%)	12 (12)	5 (14)
– Other, n (%) [‡]	3 (3)	3 (8)

[†]Bolus or continuous infusion.

[‡]Including oral, intramuscular and intra-articular.

PCA: Patient-controlled analgesia.

have been precipitated by other factors, such as underlying disease, an inherent (genetic) or acquired increased sensitivity to opioids (an acquired increase in opioid sensitivity has been observed after repetitive hypoxic events in children) [114], pharmacokinetic and pharmacodynamics drug interactions (e.g., the combination of opioids and sedatives may enhance the probability of respiratory depression) and genetic polymorphisms of genes involved in drug metabolism [2,3]. Our analysis indicates that opioid sensitivity and OIRD is difficult to predict in individual patients. We therefore advise careful titration of the opioid to effect, with meticulous and preferably continuous monitoring of respiratory variables and level of consciousness. Furthermore, independent of the level of monitoring, it is equally important to take into account the known pharmacokinetics and dynamics of the opioid as well as all patient factors that may enhance the opioid's effects on breathing.

• Comparison with case reports on OIRD in pediatrics & chronic pain

In two previous reports, we presented an analysis of case reports in pediatric and chronic pain patients published since 1980 [2,3]. In our

review of pediatric case reports, we retrieved 27 cases in patients 12 years of age or younger [2]. In eight cases, OIRD was due to an inadvertent overdose, seven of which were fatal. In the remaining 19 patients, the most notable patterns were:

- Morphine administration in patients with renal failure causing the accumulation of active metabolites;
- Morphine intoxication following codeine administration in eight patients with *CYP2D6* gene polymorphisms associated with the ultrarapid metabolizer phenotype;
- OIRD in patients following adenotonsillectomy for recurrent tonsillitis and/or obstructive sleep apnea.

In 42 cases of OIRD in chronic pain patients [3], cases published before the year 2000 predominantly involved morphine in oncology patients whereas cases published since 2000 predominantly involved methadone, transdermal fentanyl and oxycodone in patients with chronic noncancer pain, most importantly musculoskeletal pain. Patient-related factors included renal failure and drug interactions on the CYP450 system.

• Case-related factors

In our current analysis, the following case-related factors were apparent:

- Morphine was the drug reported most frequently followed by the phenylpiperidines fentanyl and sufentanil, reflecting their frequency of use in the perioperative setting. The replacement of alfentanil by remifentanil apparent in pre-2000 to post-2000 cases reflects the change in popularity and availability of these agents in local practice;
- Perioperative (postanesthesia care unit and ward) and obstetrics accounted for greater than 85% of the locations of OIRD. The appearance of remifentanil-induced OIRD after 2000 in obstetric wards reflects a clinical trend in which remifentanil PCA replaces local anesthetic-based epidural analgesia for the treatment of labor pain [107,108,110]. Focus on the respiratory effects of remifentanil PCA for labor pain is required as it is our belief that this form of analgesia will increase significantly in the upcoming years;
- Neuraxial opioid administration and single intravenous administrations accounted for more than 70% of the cases.

• Patient-related factors

In our current analysis, the following patient-related factors were apparent:

- A greater number of women experienced OIRD in cases since 2000. As suggested by a recent meta-analysis, women have a greater opioid sensitivity compared with men [115]. This regards to both analgesia and respiratory depression [116]. The meta-analysis showed that greater opioid sensitivity in females became apparent during prolonged opioid treatment periods (>24 h);
- The age range of OIRD was 14–85 years and not different in pre- and post-2000 periods. Our analysis revealed that advanced age was not a risk factor for OIRD (see below);
- Comorbidities played a causal role in the development of OIRD in 31% (pre-2000) and 41% (post-2000) of cases. Most prevalent were SDB (17 cases) and renal impairment (nine cases). Renal impairment will cause the accumulation of toxic metabolites (e.g., the accumulation of morphine-6-glucuronide following morphine

treatment) and requires providers to prescribe opioids and their active metabolites that are cleared through nonrenal pathways. In children, SDB has been associated with an increased analgesic sensitivity to opioids [114]. Rodents exposed to recurrent hypoxic episodes show a greater respiratory sensitivity to opioids [117]. These are important observations and suggest a link between recurrent hypoxic events and OIRD, possibly also in the adult population;

- Seven cases of tramadol-induced respiratory depression are reported [65,89,97,103–105], most of which are related to gene duplication of the CYP2D6 system (i.e., rapid and ultra-rapid metabolizers) causing an excess of the active metabolite *O*-desmethyl tramadol inducing respiratory depression, even when just a low dose was administered. *O*-desmethyl tramadol has a much greater affinity for the μ -opioid receptor than the parent drug.

In an approach similar to ours, Lee and Domino recently published a list of factors associated with OIRD from the ASA Closed Claims Project Database (CCDB) related to malpractice lawsuits during treatment of acute pain from 1990 to 2009 [118]. Although the inclusion criteria for our data sets differ (published case reports vs cases related to claims; global reports vs US-based cases) there is agreement among risk factors associated with OIRD. In 86 cases, respiratory depression associated factors included neuraxial pain therapy, evidence of sleep apnea and co-medication (i.e., multimodal pain therapy and addition of nonopioid sedatives). In contrast to our findings, PCA played an appreciable role as cause of OIRD especially when combined with other (non-neuraxial) modes of pain therapy. In a third of cases, involvement of more than one physician in prescribing opioids was associated with respiratory depression. As often described, poor communication between prescribing physicians and nurses mentioned as contributing to unrecognized and serious respiratory depression. Finally, in common with our findings, advanced age was not a factor associated with respiratory depression. This may be related to the higher acceptance of a fatal outcome from pain therapy in elderly (and possibly sicker) patients compared with younger patients.

Prevalance of OIRD

Our analysis of case reports gives us a reliable assessment of both case- and patient-related

factors of OIRD. However, our analysis does not provide an insight in the number of patients (i.e., prevalence) experiencing fatal or nonfatal OIRD. The number of patients described ($n = 135$) is just a small fraction of the total number of patients that we know to experience OIRD. Also US data from malpractice claims provide little information in this respect. For example, Lee and Domino describe only 86 cases (period 1990–2006) in adult perioperative patients, while Subramanyam *et al.* [119] describe 16 and six pediatric patients following tonsillectomy that had opioid-related fatal and nonfatal respiratory depression, respectively. A recent publication states that from 1999 to 2010, the number of yearly deaths due to opioid overdose has increased from 1.4 to 5.3 per 100,000 (US population) or approximately 16,000 individuals in 2010 [120]. The increase over time paralleled the sale of opioids and admissions for opioid abuse treatment. Evidently, this number includes opioid abuse/misuse outside the medical setting, opioid treatment for chronic and acute pain and palliative case, but indicates the enormity of the problem. We estimate that nonfatal occurrences of OIRD must be a factor of at least 100 greater.

Conclusion

In aggregate, the CCDB data, this analysis of case reports in the acute setting, and our previous analyses in chronic pain patients and pediatrics, support the theory that OIRD is a significant cause of preventable morbidity and mortality. Despite the presence of associated factors, our analyses indicate that OIRD is difficult to predict in any one patient and we therefore recommend that as a first step in the prevention of OIRD, to carefully titrate the patient to effect. Moreover, all patients that receive an opioid in the acute setting must be adequately observed and continually electronically monitored. Other measures that may prevent OIRD include adequate education of all involved in the deliverance of pain therapy and optimizing communication between caregivers (nurses and doctors). We are aware that these recommendations are challenging and costly, but not as costly as the inadvertent loss of life from well-intended but lethal opioid therapy.

Evidently, our analysis prompts further research in the analysis of currently available large data sets on OIRD, such as may be available from hospital

data management systems or insurance companies. This will result in specific factors that may be associated or predictive of OIRD. Additionally, we would like to encourage physicians to perform prospective studies on OIRD, for example, in the acute hospital setting (recovery room/PACU) and also in the wards where opioids are often administered without proper monitoring. Studies as suggested here will bring us forward in the continuous struggle to make opioid therapy safer.

Future perspective

We are looking forward to the development of specific nonopioid drugs that prevent respiratory depression during opioid therapy. Several types of drugs are being developed including ampakines and BK-channel blockers. These agents stimulate breathing through activation of respiratory centers at central (i.e., within the CNS) or peripheral (i.e., at the carotid bodies) sites, independent of any action at the opioid receptors, and consequently offset the reduced breathing from opioids without affecting analgesia. Possibly combining these drugs with common opioids will reduce the probability of opioid-related morbidity and mortality. Still vigilance remains required and development of sophisticated monitoring tools in patients taking potent opioids and patients with comorbidity prone to develop respiratory depression is additionally required. We envision the development of telemetric monitors of the cardiorespiratory system attached to smart sensors embedded in watches, smartphones or garments. Yet again, these approaches may not result in the (false) feeling of safety, as opioids remain potentially fatal under all conditions.

Financial & competing interests disclosure

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