Reviews

Opioids, ventilation and acute pain management

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SUMMARY

Despite the increasing use of a variety of different analgesic strategies, opioids continue as the mainstay for management of moderate to severe acute pain. However, concerns remain about their potential adverse effects on ventilation. The most commonly used term, respiratory depression, only describes part of that risk. Opioid-induced ventilatory impairment (OIVI) is a more complete term encompassing opioid-induced central respiratory depression (decreased respiratory drive), decreased level of consciousness (sedation) and upper airway obstruction, all of which, alone or in combination, may result in decreased alveolar ventilation and increased arterial carbon dioxide levels.

Concerns about OIVI are warranted, as deaths related to opioid administration in the acute pain setting continue to be reported. Risks are often said to be higher in patients with obstructive sleep apnoea. However, the tendency to use the term 'obstructive sleep apnoea' to encompass the much broader spectrum of sleep- and obesity-related hypoventilation syndromes and the related misuse of terminology in papers relating to obstructive sleep apnoea and sleep-disordered breathing remain significant problems in discussions of opioid-related effects.

Opioids given for management of acute pain must be titrated to effect for each patient. However, strategies aiming for better pain scores alone, without highlighting the need for appropriate monitoring of OIVI, can and will lead to an increase in adverse events. Therefore, all patients must be monitored appropriately for OIVI (at the very least using sedation scores as a '6th vital sign') so that it can be detected at an early stage and appropriate interventions triggered.

Key Words: acute pain management, opioid analgesics, postoperative pain, respiratory depression, sleep-disordered breathing, obstructive sleep apnoea

Despite the increasing use of a variety of different analgesic drugs and techniques, opioids continue

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Accepted for publication on April 18, 2011.

to be the mainstay for management of moderate to severe acute pain after surgery, injury and some acute medical illnesses. However, concerns remain about their potential adverse effects on ventilation in this setting. This applies to all patients, but especially to those who may be more sensitive to opioids, including the elderly and patients with sleep-disordered breathing (SDB).

It is important to recognise that the most commonly used term, respiratory depression, only describes part of the risk. Opioid-induced ventilatory impairment (OIVI) is a more complete term encompassing opioid-induced central respiratory depression (decreased respiratory drive), decreased level of consciousness (sedation) and upper airway obstruction, all of which, alone or in combination, may result in decreased alveolar ventilation and increased arterial carbon dioxide (P_aCO_2) levels. The

term OIVI will therefore be used in preference to respiratory depression in this article unless referring specifically to respiratory drive.

Concerns about OIVI are warranted, given that deaths related to opioid administration in the acute pain setting continue to be reported, in particular relating to patients given intravenous patient-controlled analgesia (IV-PCA) or neuraxial opioids after surgery[1,2]. Whether or not patients receiving opioids by specific routes, including via IV-PCA, are truly more at risk is discussed later.

This review will first look at how opioids can affect ventilation and possible effects in patients with SDB, and then at the risk of OIVI after opioid administration for the treatment of acute pain including in patients with SDB. Finally, possible strategies that may help to reduce this risk will be discussed.

While the principles outlined will apply to patients given opioids for management of acute pain from any cause, including pain resulting from injury or an acute medical illness, most of the relevant literature to date relates to surgical inpatients. The focus of this review will therefore be on opioids and ventilation in the postoperative setting.

OPIOIDS AND VENTILATION
Physiology of opioid-induced ventilatory impairment

The physiological effects of opioids on ventilation are complex and the avoidance of adverse clinical outcomes requires a clear understanding of the mechanisms by which systemic opioids may affect the central nervous system (CNS). It should be remembered that in clinical practice, the depressant effects of opioids are often potentiated by the presence of other CNS depressant drugs (e.g. anaesthetic agents, benzodiazepines, anti-depressants), amplified by fatigue in the patient (e.g. from illness or sleep deprivation), and compounded by concurrent medical conditions – in particular obstructive sleep apnoea (OSA), abdominal distension, pulmonary conditions such as chronic obstructive pulmonary disease and obesity.

Although interlinked, the depressant effects of opioids on the CNS can be divided into three main areas:
1. depression of respiratory drive – 'central respiratory depression',
2. depression of consciousness – 'sedation',
3. depression of supraglottic airway muscle tone – 'obstruction'.

These three factors combine to decrease ventilation and hence reduce pulmonary gas exchange resulting in hypoxia and hypercapnia. Hypercapnia has a direct depressant effect on the CNS, further exacerbating opioid (and other) effects. This creates a dangerous clinical environment where physiologic reserve is compromised and patients can very rapidly deteriorate. Thus, as emphasised elsewhere in this article, early detection and intervention in response to signs of CNS depression is paramount.

Decreased respiratory drive – central respiratory depression

Central respiratory depression is the most commonly referred to serious side-effect of opioid use in the acute pain environment. Although often explained as an alteration in the 'set point' for carbon-dioxide driven ventilatory drive in the brainstem, the action of opioids is more precisely described as enhancing the activity of inhibitory neurones in the deeper rhythm generating centres . This has been described as 'controller gain' by White and refers to the effects of opioids on both hypercapnia and hypoxia[3].

In normal circumstances, intrinsic cyclical activity in the inspiratory centre is affected by excitatory fibres from the chemosensitive area of the ventral medulla (responding to P_aCO_2 via cerebrospinal fluid [CSF] pH) and modulated by inhibitory GABA-ergic neurones amongst others. Opioid-induced central respiratory depression is mediated predominantly by mu-opioid receptor effects[4] but also by kappa-opioid receptor activity[5] on the inspiratory centre to reduce the frequency of respiration. The stimulatory effect on respiration from the chemosensitive area for a given CSF pH is thus diminished and a higher P_aCO_2 (and hence lower pH) is required to overcome this. The intensity and duration of this effect depends on a multitude of factors, but from a pharmacological point of view, relates to a drug's potency, dose, route of administration, distribution to the CNS and pharmacodynamics (including opioid tolerance and age). Much of the individual drug pharmacology is beyond the scope of this article. Opioids have little direct effect on the triggers to end the inspiratory cycle. This implies that when patients with OIVI have elevated P_aCO_2 and normal or high-normal respiratory rates, other contributing factors (e.g. abdominal splinting) must also be considered.

In normal circumstances, P_aO_2 does not contribute significantly to respiratory drive. Inputs to the inspiratory centre from the carotid and aortic bodies via the glossopharyngeal nerves increase as P_aO_2 falls below normal levels, especially below a P_aO_2 of approximately 60 mmHg. However, the stimulatory

effect on respiration is usually overwhelmed by the sensitivity to CO_2. Thus hypoxia is neither a good stimulus for respiration nor an early index of OIVI, although it may be an early sign of ventilatory insufficiency from other causes such as atelectasis or pulmonary oedema.

Opioids also enhance vagal cardioinhibitory activity, causing bradycardia and a reduction in sinus arrhythmia. Clinically this is most obviously seen with the potent mu-receptor agonist remifentanil. This effect is mediated by disinhibition of central cardiac vagal neurones by inhibiting spontaneous inhibitory GABA-ergic and glycinergic synaptic input. It is by this pathway that the inspiratory centre driven sinus arrhythmia (increased heart rate during inspiration) is obtunded by opioids.

Naloxone reversal of opioid activity is due to its non-selective competitive antagonism at mu-, delta- and kappa-opioid receptors. Its extent and duration of effect is highly variable[6] and will depend on the type and dose of opioid amongst other factors. However, when given in a sufficient dose to reverse opioid-induced respiratory depression, the duration of effect is approximately 30 minutes[7,8]. In clinical practice, this usually allows sufficient time for effect-site opioid concentrations to decline, depending upon the cumulative dose and kinetics of the opioid in question.

Respiratory neuronal activity is enhanced by serotonin through its action on $5-HT_{4A}$ and $5-HT_{1A/7}$ receptors. This opens the possibility for selective serotonergic agonists to counteract central opioid-induced respiratory depression while leaving analgesia intact[9]. Data from animal studies suggest that both agonist classes counteract mu-opioid agonist respiratory depression while not suppressing antinociception, with the $5-HT_{1A/7}$ receptor agonists stimulating respiration[10,11]. Serotonin agonists may also counteract opioid-induced bradycardia and hypotension. Unfortunately, studies in human volunteers using a partial agonist to the $5-HT_{1A}$ receptor have not been so promising, with no effect of buspirone on analgesia or respiratory depression: however there was a not surprising increase in the incidence of nausea[12].

Decreased consciousness – sedation

The term 'narcotic' has been used for centuries to refer to opioids because of their sedative effect, which is independent of that induced by hypercapnia. In clinical practice, sedation caused by opioids has proven challenging to measure, in part because the sedative effects influence both arousal (response to a stimulus) and concentration (ability to remain alert)[13].

Neurophysiologically, these clinical effects are due to the actions of opioids via mu-opioid receptors in the hypothalamus, possibly on the hypocretin/orexin system, to increase arousal thresholds and reduce wakefulness[14]. This is achieved by both pre- and post-synaptic actions. In clinical practice, the sedative effects of opioids may manifest earlier than the respiratory effects, especially in the presence of other CNS depressants, and thus constitute a useful early warning sign[15,16]. The importance of sedation as a risk factor is that delayed arousal per se may increase the risk of aspiration or the failure to self-correct airway obstruction (see below).

Hypercapnia itself can lead to CNS depression, although individual responses are variable. Sedation leading to unconsciousness occurs with P_aCO_2 levels ranging from 48 to 148 mmHg[17]. A case report of an awake but inadvertently paralysed patient identified loss of consciousness with a P_aCO_2 of 130 mmHg (and a corresponding bispectral index of 35 to 40)[18].

Decreased oropharyngeal muscle tone – obstruction

The importance of upper airway obstruction in OIVI has been emphasised recently by Overdyk and Hillman[19]. The increased attention to the clinical problems of OSA has identified a group of patients who are at risk of upper airway collapse during normal sleep, which may be exacerbated by sedatives such as opioids[3,20]. The propensity of sedatives to decrease upper airway muscle tone in 'normal' patients challenges the traditional concepts of opioid-induced respiratory depression. Both propofol[21] and opioids[22] have been shown to suppress central tonic outflow to the genioglossus muscle, which is the primary airway dilator. Therefore, in addition to central respiratory depression and sedation, opioid-induced loss of airway tone may lead to upper airway obstruction. The interaction between all these potential effects is, however, complex, especially during sleep, and it cannot be assumed that they will always be additive.

OPIOIDS, OBESITY AND SLEEP-DISORDERED BREATHING

The misuse of terminology in papers relating to the perioperative implications and understanding of OSA and SDB is a significant problem[23]. This has particular relevance for any discussion regarding opioids. For example, the abstract of an otherwise relevant paper states: "Despite fewer obstructions, OSA was worse during remifentanil infusion because of a marked increase in the number of central apneas"[24], thus confusing central apnoea and OSA. 'Obstructive sleep apnoea' is, commonly and

mistakenly, equated by many authors with obesity hypoventilation syndromes and central apnoea syndromes, and indeed the whole complex spectrum of SDB as well as the entire continuum of severity. These misnomers and oversimplifications are, at best, unhelpful and lead to confusion amongst clinicians and researchers. At worst, they may ultimately lead to a misdirection of therapies and result in adverse outcomes. In the example cited above[24], an appropriate therapy if the 'OSA was worse [with opioid]' might be continuous positive airway pressure (CPAP), but this would be of little benefit where the SDB was predominantly central in nature, as occurred in that study.

The implications are also significant when considering the potential effect of opioids on respiration during sleep. The inter-relationships between sleep, obesity and respiratory function are very complex[25,26]. It has been acknowledged that even amongst sleep physicians the distinction between severe obstructive sleep apnoea, hypopnoea and obesity hypoventilation syndromes is confused[27]. Similarly, the differential effects of various sleep stages on central respiratory control, the respiratory pump muscles and the upper airway are also highly variable and complex[28,29]. The addition of opioids and/or the pain for which those opioids are usually prescribed adds yet other layers of complexity to the equation[25,30]. This means that prediction of the predominant respiratory effect of any given analgesic dose of opioid for any given individual at any given postoperative (or other) time is very difficult.

It is commonly assumed that opioids will worsen upper airway obstruction in patients with OSA and that altered sleep architecture in the immediate postoperative period, perhaps also partly the consequence of opioid analgesia, will result in subsequent 'rapid eye movement (REM) rebound', which in turn will also contribute to an exacerbation of the OSA. This belief is based on the assumption that OSA is usually worse during REM sleep and that REM rebound is a significant postoperative occurrence. However, there is conflicting evidence regarding these assumptions and so they should not be held as dogma.

The end result of any influential factor such as sleep stage and/or opioid administration on alveolar ventilation will depend on the differential influence on respiratory control, pump muscles and upper airway resistance. If the respiratory pump generates enough negative intraluminal pressure in the upper airway to result in airway collapse, then obstructive apnoea/hypopnoea will occur. However, if the influential factor results in a larger decrement in

pump function (decreased respiratory muscle power and/or central respiratory drive) than upper airway muscle tone, the negative airway pressure and therefore tendency to collapse will be reduced. This is thought to be the mechanism for a lower likelihood of apnoeic events commonly seen during slow wave sleep in OSA sufferers[28] and even during REM sleep in some individuals[29]. While the end result may still be a reduction in alveolar ventilation for many individuals, for others with a primary tendency to obstruction it may not. If the balance falls strongly towards central or restrictive hypoventilation (e.g. from obesity or abdominal distension limiting thoracic cage expansion), as is likely with obesity hypoventilation syndromes, then management will be very different from management of a situation where obstruction is the predominant problem.

These complex differential effects probably explain, at least in part, the conflicting evidence that has emerged regarding the effects of both acute and chronic opioid administration on ventilation during sleep in subjects with and without OSA. SDB in patients receiving chronic opioid therapy has been the subject of several recent investigations and reviews[25,30-35] and found to be highly prevalent. Although obstructive events are more common in some studies, in most there is a marked preponderance of central apnoea and irregular ('ataxic') breathing. This results in hypoxaemia, in some subjects even during wakefulness, and appears to be opioid dose dependent.

Fewer data are available regarding the effect of acute opioid administration on ventilation during sleep. However, the study by Bernards et al[24] examined the effect of an analgesic dose of remifentanil given to volunteers with moderate OSA and found that OSA was reduced while central apnoeas became predominant. They suggested the former effect may have been the result of decreased REM sleep, and this was supported by the remifentanil group having some REM-predominance of their underlying OSA. However, it has previously been shown in several studies that 50% of OSA sufferers have non-REM-predominant apnoea in terms of event numbers, and differences in event duration and severity of desaturation are also not of a clinically significant nature for the majority of patients[36-38]. It is therefore possible in the subjects of Bernards' study that the reduction in OSA was, at least in part, the result of an alteration in the balance of respiratory pump and upper airway muscle activity as described above.

Caution is therefore also required when interpreting the potential effect of any late

postoperative REM rebound. For the majority of patients with mild to moderate SDB of a purely obstructive nature, perioperative alterations in sleep architecture resulting from opioids or any other factor will likely have relatively little important respiratory effect overall. REM rebound could theoretically be more important for morbidly obese individuals with obesity hypoventilation syndromes, for some of whom REM produces clinically significant prolongation of apnoeas and worse desaturation. REM rebound, however, has been an inconsistent finding in studies of postoperative sleep. There have been two clinical studies in which a rebound was demonstrated[39,40], but these findings are not supported by other earlier investigations[41-47]. One of the supportive studies reporting REM rebound did not involve standard polysomnographic techniques or sleep staging and oximetry artefact was not addressed, leaving the results open to doubt[40]. Finally, should REM rebound occur in the postoperative setting, it usually represents a small percentage of total sleep time[39,40], so that any risk additional to the patient's usual long-term nightly risk associated with SDB would be limited.

The individual effect of opioids is influenced by pharmacological factors as well. Obesity[48] and possibly SDB[49,50] may alter the kinetics and dynamics of opioids, as well as other sedatives, adding yet further complexity to the situation. Increasing age has been well described as increasing the sensitivity to both the analgesic and central depressant effects of opioids[16,51].

Assessing the impact of OSA or SDB on individual patients prescribed perioperative opioids is complex and not dependent on a single diagnosis of 'OSA'. The ultimate net influence of obesity, body position, sleep state and stage, pre-existing SDB, opioids and other sedatives, pain, fasting and other perioperative or intensive care factors on alveolar ventilation deserves far more considered scrutiny. This applies both clinically and in research. In this context, generic guidelines are rendered rather unhelpful and there must be a return to an emphasis on the clinical basics of individual patient assessment and careful titration of agents, preferably using multimodal analgesia to limit opioid requirement where possible. Preventive and monitoring strategies must also be applied on an individual patient basis.

THE RISK OF OPIOID-INDUCED VENTILATORY IMPAIRMENT

The true incidence of OIVI (including respiratory depression) associated with opioid administration in the acute pain setting is almost impossible to determine from published studies because of differences in the way in which assessments are made. While most authors use a decrease in respiratory rate as an indicator (albeit not necessarily an accurate one) of central respiratory depression, others measure arterial carbon dioxide (P_aCO_2) or oxygen saturation levels, or requirements for naloxone, all of which are the end results of OIVI. Until there are uniform definitions of respiratory depression as a component of OIVI, meaningful comparisons cannot easily be made.

An earlier review of randomised-controlled trials reported the incidences of OIVI (described as 'respiratory depression') associated with different routes of opioid administration. These were: intra-muscular (IM)/intravenous (IV) opioids 2.4%; IV-PCA 1.8%, epidural analgesia 1.9% and intra-thecal opioids 1.6%[52]. However, the ways in which respiratory depression was defined were not given.

A later paper reviewed results from all trials (including cohort studies, case-controlled studies and audit reports as well as randomised-controlled trials), and also reported differences according to route of opioid administration as well as the criteria used by the different authors to define respiratory depression[53]. The differences were considerable. The incidence of respiratory depression reported for IM opioid analgesia was 0.8% and 37% using decreased respiratory rate (an indicator of decreased respiratory drive) and oxygen desaturation (an end-result of OIVI), respectively, as indicators. Using the same measures, the corresponding rates for IV-PCA were 1.2% and 11.5%, and for epidural analgesia 1.1% and 15.1%.

Interestingly, while these results would suggest that the greatest risk of OIVI lies with IM opioid analgesia when a decrease in oxygen saturation was used as the measure, the same authors also reported that pain relief was significantly worse with IM compared with IV-PCA or epidural analgesia[54]. The mean percentage of patients with moderate-severe pain was 67.2% for IM analgesia, 35.8% for IV-PCA and 20.9% for epidural analgesia. The results for severe pain were 29.1%, 10.4% and 7.8% respectively. That is, 96.3% of patients given IM opioids for management of their acute pain had moderate-severe or severe pain, suggesting that these patients may have received much lower doses of opioids than patients using IV-PCA. It is therefore probably unlikely that these patients would have a greater risk of OIVI (see later for comments on reliability of oxygen saturation as a measure of OIVI). These data highlight the fact that there are many reasons other than opioids for hypoxaemia, or indeed

respiratory failure, especially in the postoperative setting[55,56].

The articles cited in the paper by Cashman and Dolin[53] included papers published up until and including 1999. Since then, concerns have been raised about the dangers associated with the use of IV-PCA, especially in patients with OSA[1,57].

However, as it is known that IV-PCA provides better pain relief than IM opioid analgesia and that opioid consumption is greater[58], it is possible that the risk of OIVI correlates better with dose of opioid received by the patient and patient-specific factors rather than route or method of administration. This means that the better the pain relief with opioids, the greater could be the risk of OIVI. Indeed, use of an unbalanced strategy for pain management, which emphasises the need for better pain management and lower pain scores by encouraging greater opioid use without stressing the need for appropriate patient monitoring, can and will lead to an increase in adverse events[15].

Therefore, all patients given opioids for acute pain should be monitored appropriately, regardless of the route of administration, and opioids should be titrated to effect in all patients. Without such monitoring, safe and effective management of acute pain using opioids is not possible. This should also ideally include patients who are not inpatients (e.g. patients given more potent opioids in larger doses after day-stay surgery or treatment in an emergency room).

Patients with sleep-disordered breathing

A common concern in patients with OSA is that they may be at increased risk of OIVI[1,57]. However, evidence of the risks associated with analgesia and SDB is surprisingly limited. It must always be remembered that opioid-related respiratory depression, possibly exacerbated during sleep (itself largely indistinguishable from opioid-related sedation unless the patient is roused), can and does occur without any pre-existing SDB (Figure 1).

A randomised study comparing the effects of saline and remifentanil infusions in volunteers with documented moderate OSA showed that remifentanil actually decreased the number of episodes of obstructive apnoea, thought to be related to the associated decrease in REM sleep, but markedly increased the number of central apnoeas recorded[24]. As noted earlier, the issue of REM suppression and REM rebound is complex but there may be a difference if opioid use is continued.

'Evidence' in the clinical setting is limited mainly to clinical case reports. The reports commonly cited
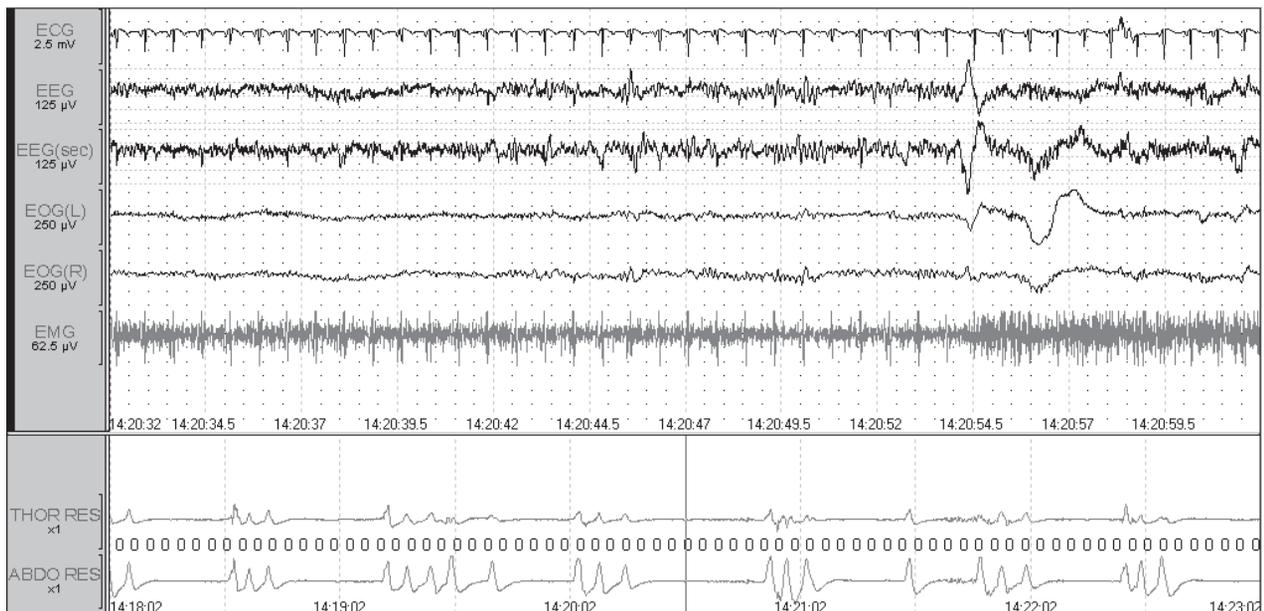

Figure 1: A recording captured during a postoperative research sleep study (Drummond GB, Loadsman JA, unpublished data) in the ward on the afternoon shortly after discharge from the post-anaesthesia care unit. The patient, aged 40 years, had a vaginal hysterectomy and tension-free vaginal tape sling and was using morphine patient-controlled analgesia. The top frame shows the electrophysiological data from a single 30-second epoch. The bottom frame shows five minutes of recording from the thoracic and abdominal inductance plethysmography bands, with the line down the centre indicating where the 30-second epoch above commences. The pulse-oximeter probe failed during the study and no data were recorded. Multiple central apnoeas, an unexpected finding, presumably opioid-related and present for a substantial proportion of the two-hour recording, can be readily identified and an arousal can be seen corresponding with resumption of breathing in the epoch displayed. ECG=electrocardiogram, EEG=electroencephalogram, EOG=electro-oculogram, EMG=submental electromyogram.

to indicate an increased risk of sometimes fatal OIVI in patients with OSA given opioids for management of their postoperative pain require caution in their interpretation.

Four of these reports involved the use of IV-PCA[59-62], another reported the deaths of three patients given postoperative bupivacaine and fentanyl epidural infusions[63], and the other a patient who died after being given IM morphine[64]. Most of the cases involved what appeared to be an over-reliance on respiratory rate as an indicator of OIVI, central respiratory depression measured by respiratory rate being only one element of OIVI. Sedation levels were not checked on a routine basis and/or the significance of increasing sedation (discussed below) was not recognised.

There is no good evidence that can be used to evaluate the effects of various postoperative analgesia techniques in patients with known OSA[65]. There is however, some information related to patients assessed as being at risk of OSA.

Patients classified as having a probable diagnosis of OSA, assessed by history, body mass index (BMI) and examination of the airway (patients with known OSA were excluded) have been shown to have more obstructive events in the postoperative period than control patients[66]. However, in patients with a BMI of greater than 28 and probable OSA, no difference in the number of respiratory events (obstructive apnoeas, hypopnoeas or central apnoeas) was found between those given IV-PCA morphine compared with those given an 'opioid-sparing' analgesic regimen (IV-PCA tramadol, parecoxib and 'rescue-only' morphine), but there was a correlation between more than 15 respiratory events/hour and central apnoeas with total morphine dose[67].

Thus there is currently no good quality evidence available to either confirm or refute an increased risk associated with postoperative opioid administration in patients with known OSA. Similarly, the evidence for increased postoperative risk in general in patients with OSA is conflicting.

Earlier studies suggested that the complication rate, at least after more major surgery, was associated with a diagnosis of OSA. For example, the overall rate (including unplanned ICU admissions, reintubations and cardiac events) after joint replacement surgery, for which opioid requirement is likely to be substantial, was reported to be higher in patients with OSA compared with patients in the control group matched for type of surgery[68]. However, this was not seen in patients after out-patient surgery where analgesic requirement is significantly less[69].

Later studies have also suggested that patients with OSA are at increased risk of postoperative complications. A retrospective matched cohort study comparing patients with diagnosed OSA and non-OSA patients (240 patients in each group) reported that patients with OSA had a higher rate of post-operative complications overall as well as total respiratory complications (most commonly low oxygen saturation levels). However, despite matching, the OSA patients had a higher prevalence of medical comorbidities and higher BMIs[70].

There is a known association between high BMI and the chance that a patient has OSA. In patients presenting for bariatric surgery, the incidence of OSA was greater than 70% and grew as BMI increased[71]. In a large retrospective review of 797 patients who underwent bariatric surgery (442 open and 355 laparoscopic procedures), postoperative pulmonary and overall complication rates were associated with open procedure, patient age and BMI, but not severity of OSA[72].

Therefore, it is probable that the risk lies more with patient factors such as body size and build, especially those who are morbidly obese, rather than the diagnosis of OSA per se[23].

STRATEGIES THAT MAY REDUCE RISK OF OIVI

Strategies that may help to reduce the risk of OIVI include:
- improved monitoring for OIVI,
- minimising use of other drugs that increase the risk of OIVI,
- appropriate documentation and interventions as needed,
- appropriate intravenous IV-PCA and other systemic opioid prescriptions.

Improved monitoring for opioid-induced ventilatory impairment

There is as yet, no consensus on the 'best' way to detect OIVI in the clinical setting. While measurement of P_aCO_2 is the most sensitive and accurate, it is not practicable in most patients. Other surrogate indicators are therefore used.

The Anesthesia Patient Safety Foundation (APSF) in the USA has been particularly active in leading discussions about how best to monitor for OIVI with a number of articles appearing in their newsletters over recent years. A workshop specifically convened by the APSF to look at improved recognition of postoperative OIVI in response to concerns about

the safety of IV-PCA, considered the sensitivity, specificity, reliability, response times and costs of a number of methods of monitoring ventilation and/or oxygenation: respiratory rate, tidal volume, continuous measurement of oxygen saturation and end-tidal CO_2, blood gas analysis, minute ventilation and chest wall impedance[1].

It was recognised that all these techniques had limitations, including continuous pulse oximetry used to measure oxygen saturation levels, especially in patients given supplemental oxygen. Nevertheless, the recommendation resulting from this workshop, and reiterated in a later APSF Newsletter[2], was that oxygen saturation should be routinely measured on a continuous basis as well as ventilation in all patients receiving IV-PCA or neuraxial opioids[1,2], or serial doses of other parenteral opioids[1].

In contrast, members of an American Society of Anesthesiologists Task Force developing guidelines for the prevention, detection and management of 'respiratory depression' associated with neuraxial opioid administration, differed and considered that pulse oximetry was not more likely to detect 'respiratory depression' than other clinical signs[73].

Of the methods of assessment looked at by the APSF, those most commonly employed in hospitals as surrogate measures of OIVI are respiratory rate and oxygen saturation; in many centres level of sedation (not included by the APSF) is also monitored. It is assumed by medical and nursing staff that these correlate with P_aCO_2 levels, which may or may not be the case as so many variables apply and therefore little if any work has been done to establish the validity of these assumptions. Under development are ways to less invasively measure blood carbon dioxide levels. These measures are discussed in more detail below.

For patients in all settings and countries to benefit regardless of the route of administration of the opioid, and regardless of whether the patient is in hospital or at home, the ideal monitor needs to be reasonably reliable, cheap and easy to use. This means that assessment methods using expensive equipment – not necessarily expense per unit cost but overall costs if required for all patients given opioids – are not necessarily the best. A simple clinical measure used for every patient wherever they are located may have greater overall benefit.

Oxygen saturation

While the recommendations of the APSF are that continuous measurement of oxygen saturation should be used in order to monitor for OIVI[1,2], oxygen saturation levels may not always be a reliable

method of detecting OIVI in the postoperative setting. Although it is an easy and noninvasive measure of blood oxygen levels, care must be taken in the interpretation of any readings. Oxygen saturation is a measure of gas exchange in the lungs and a surrogate measure only of respiratory drive[6]. If the patient is receiving supplemental oxygen, the added oxygen may mask deterioration in respiratory function and oxygen saturation levels may remain within acceptable limits even in the presence of severe OIVI.

In addition to the lack of sensitivity when supplemental oxygen is administered, there are many possible reasons other than opioids for hypoxaemia. As noted earlier, when measurement of oxygen saturation was used as an indicator of OIVI, the incidence was three times as high in patients given IM opioids compared with those given IV-PCA despite significantly better pain relief with IV-PCA[53]. More likely reasons for postoperative hypoxia other than OIVI would be atelectasis (e.g. resulting from an inability to cough or take deep breaths after surgery), obesity, fluid overload or pre-existing chronic obstructive pulmonary disease[55]. As noted in the studies from the 1980s and 1990s listed below, patients can be hypoxaemic without having OIVI.

Supplemental oxygen

The routine use of supplemental oxygen in patients after surgery, particularly major surgery, is common in many countries. However, it has been suggested that this should not be the case because it may abolish the increased respiratory drive in response to hypoxia should OIVI occur, as well as artificially maintain oxygen saturation levels even in the presence of significant OIVI[2,57]. It has been argued that its use should therefore be justified in each patient[2].

However, there are many benefits in the postoperative period, after major surgery at least, from using supplemental oxygen to maintain better oxygen saturation levels. In addition, supplemental oxygen will not mask increasing sedation resulting from opioid-induced CNS depression and, if OIVI is severe, additional CNS depression due to carbon dioxide 'narcosis' (see earlier discussion).

Hypoxia after major surgery is common and has many causes, but if due to the patient receiving opioids, then it is much more likely to result from obstructive and central apnoea occurring when the patient is asleep, rather than a decrease in respiratory rate[74-76].

Studies of humans after major operations have shown that such hypoxaemia may be related to the

development of myocardial ischaemia, tachycardia and cardiac arrhythmias, as well as changes in cognitive function and confusion[76-83]. Administration of supplemental oxygen can lead to a reduction in heart rate in patients with a tachycardia of greater than 90 beats/minute[84] and may be effective in treating postoperative delirium associated with hypoxaemia[81].

Finally, if a patient develops OIVI, the rate of rise of arterial carbon dioxide levels that follows hypoventilation is relatively slow; significant hypoxia, on the other hand, occurs more rapidly (within two to three minutes)[1]. This has been raised as a reason not to use supplemental oxygen as hypoxia could be detected quickly[1]. However, the converse could also be true. By developing more rapidly, hypoxia could lead to patient harm more quickly, especially if it is the final event after prolonged OIVI reflecting ultimate loss of compensation. Maintaining better oxygen saturation levels by using supplemental oxygen may allow more time for OIVI to be detected (e.g. by regular monitoring of a patient's level of sedation – see below) and appropriate action taken.

Respiratory rate vs increasing sedation

Traditionally, in patients receiving opioids, respiratory rate has been monitored and used as a surrogate measure of respiratory drive (central respiratory depression). However, it is known that a normal respiratory rate may co-exist with hypercapnia[85,86]. This means that measurement of respiratory rate can be an unreliable guide to OIVI.

As noted earlier, in excessive doses (relative or absolute) and regardless of route of administration, opioids cause CNS depression. This in turn can lead to central respiratory depression (decreased central CO_2 responsiveness resulting in hypoventilation and elevated P_aCO_2 levels) as well as a progressive decrease in conscious state and loss of tone in upper airway muscles which can result in upper airway obstruction. In the case of severe OIVI and very high P_aCO_2 levels, carbon dioxide narcosis will contribute to and exacerbate the CNS depression.

As noted above, it is known that OIVI is not always accompanied by a decrease in respiratory rate. However, it is usually accompanied by another sign of CNS depression – a decrease in the patient's level of consciousness (increasing sedation). This association was first reported by Ready et al[86] in an audit of the first year of their Acute Pain Service where four elderly patients had developed severe OIVI after administration of epidural morphine. Of these patients, two were very sedated and their P_aCO_2 levels were 63 and 66 mmHg; however the

lowest recorded respiratory rates were only 11 and 8 breaths/minute respectively. The other two patients were unconscious; P_aCO_2 levels were 85 and 95 mmHg and their respective lowest recorded respiratory rates were 8 and 12 breaths/minute. Ready et al[87] then developed and used sedation scores (see below) to routinely monitor for OIVI in all patients given opioids.

Other publications have confirmed this correlation. Vila et al[15] described their results before and after the hospital-wide introduction of pain management standards. These standards were designed to improve pain relief in a cancer setting by encouraging administration of opioids as needed in order to achieve satisfactory pain scores. Unfortunately, this intervention resulted in a two-fold increase in the risk of OIVI. Of the 29 patients who developed OIVI, only three had a respiratory rate of less than 12 breaths/minute. However, 27 of the 29 were noted to have altered levels of consciousness prior to the respiratory event. The authors concluded that there was not a predictable decrease in respiratory rate associated with respiratory depression (i.e. OIVI) and highlighted the risk of titrating opioids to achieve a desirable pain score only without other appropriate patient monitoring.

In another publication, Shapiro et al[88] audited 1524 patients treated by their Acute Pain Service who received IV-PCA or neuraxial morphine for postoperative pain relief. 'Respiratory depression' was defined as a respiratory rate of <10 breaths/minute and/or a sedation score of 2 (defined as 'asleep but easily roused'). They reported that 13 patients (1.86%) developed respiratory depression; all had respiratory rates of <10 breaths/minute (in contrast to the earlier study) and 11 also had sedation scores of 2. However, a sedation score of 2 as defined in this paper may not always be indicative of CNS depression as it may be the inability to stay awake after being roused, albeit easily, that could be the key (see below). Their sedation score of 1, defined as 'drowsy', could actually indicate a greater degree of CNS depression than a patient who is sleeping but wakes easily and stays awake, so their scoring system may not always be able to indicate progressive CNS depression.

Checking a patient's level of alertness was considered by the American Society of Anesthesiologists Task Force to be important in the detection of OIVI in patients given neuraxial opioids, as well as assessments of adequacy of ventilation and oxygenation[73]. However, it also recommended that sleeping patients only be woken

if there was concern about other signs. This leaves the patient open to risk because if no attempt is made to rouse a sleeping patient, it would be possible for increasing sedation to be missed.

Sedation scores

Thus, the best clinical indicator of early OIVI is increasing sedation, a general measure of CNS depression. This can be monitored using a simple sedation score – a '6th vital sign', pain being the 5th. Like other potential monitors for OIVI, measurement of increasing sedation suffers from a lack of specificity and sensitivity. However, it is cheap, simple to teach and easy to use.

A number of different sedation scoring systems are available. Whichever is used, it must represent a sensible progression of CNS depression – that is, a progressive decrease in a patient's conscious state (increasing sedation) and not necessarily other CNS changes such as cognitive function or whether or not the patient is confused. Furthermore, sedation scoring systems should be standardised across all hospitals in a region, to avoid confusion and errors in communication.

One commonly used system for sedation scores is that outlined in Table 1[89,90], derived from the sedation score classification initially developed by Ready et al[87]. Note that it indicates patients must be roused to assess their level of sedation. Opinion about incorporation of category '1S' into this classification varies. In some centres, sedation scores of 1S are included as part of the scoring system and used to indicate that the ability to rouse sleeping patients at night does not equate to shaking them to wakefulness, but rather identifying that they will stir in response to mild stimuli, thus patient sleep need not be disturbed unnecessarily. In other institutions, a score of 1S is not used in the belief that it might be too easy to miss a sedation score of 2 – the key to recognition of early OIVI and triggering an appropriate intervention. This latter approach may be the safer option. Use of a sedation score of 'S' to indicate that the patient is sleeping may mean

that no attempt is made to wake the patient. This is the least safe option as even severe OIVI may be missed. In the authors' experience, when P_aCO_2 measurements have been done on patients with a sedation score of 2 (as defined in Table 1), the levels tend to be higher than 55 mmHg.

This simple system can be taught to patients given opioids to take at home, as well as family and friends who may be caring for them. They can be instructed to not take any further opioid if they (or their carers) note that they are sleepy and having difficulty staying awake. Should they then require further opioid, they can be told that the dose they take must be reduced.

Measurement of carbon dioxide levels

Less invasive measures of carbon dioxide levels are available but currently not in widespread use. These include bedside capnometry devices, which work by sampling expired carbon dioxide through modified nasal prongs and may be used while administering supplemental oxygen, and techniques used to measure transcutaneous CO_2[85,91,92]. The practical routine clinical use of such devices is still in evolution and has many barriers to overcome, including reliability, cost and patient comfort[93].

Minimising use of other drugs that increase the risk of OIVI

Concurrent administration of sedatives or drugs with sedative side-effects (e.g. benzodiazepines, promethazine, clonidine) is known to increase the risk of OIVI[16] and will also interfere with the use of sedation scoring as an indicator of OIVI. For these reasons they should be avoided where possible unless indicated for prevention of withdrawal – for example, benzodiazepine withdrawal or treatment of alcohol withdrawal, or when used as part of a carefully managed multi-modal analgesia strategy (e.g. clonidine).

Appropriate documentation and interventions as needed

If OIVI related to opioid administration is detected and treated at an early stage it will increase the chance of avoiding significant and permanent patient harm. Therefore, as well as appropriate monitoring, there must also be a means whereby nursing staff can record sedation scores, respiratory rate and pain scores at prescribed intervals as and respond to inadequate analgesia and early OIVI (i.e. titrate opioid analgesia appropriately for each patient). There is no good evidence on which to base ideal frequency of observations. With PCA and neuraxial opioids, where opioids are

TABLE 1
Sedation scores

0	awake, alert
1	mild sedation, easy to rouse
1S*	asleep, easy to rouse
2	moderate sedation, easy to rouse, unable to remain awake
3	difficult to rouse

* May not be used in some centres where a score of 1 is used whether or not the patient is asleep.

either self-administered by the patient at a variable rate or delivered by continuous infusion, hourly observations for the first eight hours after commencement followed by two-hourly observations have been suggested[90]. Any monitoring strategy demands the availability of appropriate and clearly defined lines of communication so that staff can relay their concerns promptly and effectively.

As noted earlier, any sedation scoring system should indicate a sensible progression of OIVI, such as the one given in Table 1. The measures of level of consciousness currently proposed by the Australian Commission on Safety and Quality in Health Care for use on their 'evidence-based adult general observation chart', called the Adult Deterioration Detection System chart[94], requires assessment of whether the patient is alert, responds to voice, responds to pain or is unresponsive. These intervals may not be sensitive enough to allow for detection of early OIVI.

If, when using the suggested sedation scoring system given in Table 1, a sedation score of 2 of more is reported, a reduction in opioid dose should be strongly considered, regardless of the patient's pain score, and sedation scores monitored at frequent intervals (e.g. hourly) until the patient is less sedated. If the patient is uncomfortable, alternative and less sedating forms of pain relief will form an important part of the analgesic regimen.

Appropriate IV-PCA and other systemic opioid prescriptions

In opioid-naïve patients, age-based dose regimens for all systemic opioids are recommended[16]. There is also some evidence to suggest other preferred parameters to be used for opioid administered by IV-PCA.

IV-PCA bolus dose

One study designed to determine the 'optimal' opioid dose randomised patients to receive 0.5 mg, 1 mg or 2 mg morphine. Most patients who self-administered 0.5 mg were unable to achieve good pain relief, while patients who received 2 mg with every demand had a high incidence of respiratory depression[95]. The conclusion was that 1 mg was the optimal dose of morphine and this is the usual recommended starting dose in opioid-naïve patients. Interestingly, patients who did not achieve good analgesia averaged only four demands per hour, despite a 'lockout' interval of five minutes which would have allowed a greater number of doses to be delivered[95]. Based on effect and adverse effects, appropriate alterations can be made to the size of the bolus dose, in preference to changes in the

lockout interval, so that IV-PCA is adjusted to suit the individual patient. In elderly patients, a 50% reduction in this dose to start with has been recommended[96].

Background infusions

In opioid-naïve patients, the routine use of background infusions markedly increases the risk of OIVI[97]. For this reason, the routine use of background infusions in opioid-naïve adults is not recommended. However, their relative safety may be improved if a patient's opioid requirements are already known.

CONCLUSIONS

In summary, when addressing the issue of the ventilatory effects of opioids, opioid-induced ventilatory impairment is a more complete term to use than opioid-induced respiratory depression as it encompasses opioid-induced central respiratory depression (decreased respiratory drive), decreased level of consciousness (sedation) and upper airway obstruction, all of which, alone or in combination, may result in decreased alveolar ventilation and increased arterial carbon dioxide (P_aCO_2) levels.

The risk of OIVI is difficult to determine, given the variety of assessment measures used in different studies. However, it may be related more to the dose of opioid given than technique of administration. In patients taking opioids on a long-term basis, as in patients with SDB, central apnoea may be a more common finding than obstructive apnoea.

In all patients however, the risk of OIVI can be reduced if appropriate and regular monitoring is undertaken. A more reliable clinical sign of early OIVI is increasing sedation; a decrease in respiratory rate may not occur even in the presence of significant hypercapnia. Therefore, sedation scores that represent a progression in CNS depression should be monitored on a regular basis and opioid doses reduced, regardless of reported pain levels, should excessive sedation occur.

While measurement of oxygen saturation may also be useful, it should be remembered that supplemental oxygen administration may mask SpO_2 as an indicator of early onset OIVI and a significant fall in oxygen saturation levels may not been seen until P_aCO_2 levels are very high.

Other strategies that can reduce the risk of OIVI include avoidance of sedative drugs (or drugs with sedative side-effects) where possible, age-based opioid dosing in opioid-naïve patients, appropriate PCA bolus doses and avoidance of PCA background infusions in opioid-naïve patients, at least until their opioid requirements are known.

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