

# Neuraxial Morphine and Respiratory Depression

## Finding the Right Balance

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### Abstract

Morphine is a drug commonly administered via the epidural or intrathecal route, and is regarded by many as the 'gold-standard' single-dose neuraxial opioid due to its postoperative analgesic efficacy and prolonged duration of action. However, respiratory depression is a recognized side effect of neuraxial morphine administered in the perioperative setting. We conducted an extensive review of articles published since 1945 that examine respiratory depression or failure associated with perioperative intrathecal or epidural morphine use.

Respiratory depression was previously thought to result from the interaction of opioid in the cerebrospinal fluid with ventral medullary opioid receptors. More recently, the preBötzinger complex located in the medulla has been identified as the site responsible for the decrease in respiratory rate following systemic administration of opioids. Neurons in the preBötzinger complex expressing neurokinin-1 receptors are selectively inhibited by opioids, and therefore are the mediators of opioid-induced respiratory depression.

Epidural, intrathecal and plasma pharmacokinetics of opioids are complex, vary between neuraxial compartments, and can even differ within the epidural space itself depending upon level of insertion. Caution should be exercised when prescribing systemic opioids (intravenous or oral) in addition to neuraxial morphine as this can compound the potential for early or delayed respiratory depression.

There is a wide range of incidences for respiratory depression following neuraxial morphine in a perioperative setting. Disparity of definitions used for the diagnosis of respiratory depression in the literature precludes identification of the exact incidence of this rare event.

The optimal neuraxial opioid dose is a balance between the conflicting demands of providing optimal analgesia while minimizing dose-related adverse effects. Dose-response studies show that neuraxial morphine appears to have an analgesic efficacy 'ceiling'. The optimal 'single-shot' intrathecal dose appears to be 0.075–0.15 mg and the ideal 'single-shot' epidural morphine dose is 2.5–3.75 mg. Analgesic efficacy studies have not been adequately powered to show differences in the incidence of clinically significant respiratory depression. Opioid antagonists such as naloxone to prevent or treat opioid-induced respiratory depression have a number of limitations. Researchers have recently focused on non-opioid drugs such as serotonin receptor agonists.

Early evidence suggests that ampakine ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid [AMPA]) receptor modulators may be effective at reducing opioid-induced respiratory depression while maintaining analgesia. Sodium/proton exchanger type 3 (NHE3) inhibitors, which act centrally on respiratory pathways, also warrant further study.

## 1. Introduction

The discovery that opioid receptors are localized within lamina II of the dorsal horn in the CNS suggested that exogenous opioids could be administered via the neuraxial route to produce analgesia.<sup>[1]</sup> A number of published reports of intrathecal<sup>[2]</sup> and epidural<sup>[3]</sup> morphine administration in humans have since been published, and in 1984 preservative-free morphine received US FDA approval for neuraxial administration. Analgesia delivered via the neuraxial route lasts longer than the systemic route, with effects persisting 12–24 hours,<sup>[4]</sup> and in some cases longer, following administration.<sup>[5]</sup> Recognized benefits of neuraxial opioids when compared with intravenous administration include better postoperative analgesia, increased functional ability, earlier ambulation and earlier return of bowel function.<sup>[6,7]</sup> Furthermore, unlike with neuraxial local anaesthetics, there is negligible motor, sensory or autonomic blockade associated with neuraxial opioids.<sup>[2,3,8]</sup>

Neuraxial morphine is now extensively used in the perioperative setting<sup>[9]</sup> due to improved analgesia, greater duration of action and dose-sparing effects when compared with its administration via the systemic route. Despite significant analgesic advantages of neuraxial morphine over systemic administration, there are a number of potential adverse effects of which respiratory depression is the most concerning. Cases of life-threatening respiratory depression were reported soon after clinical administration of neuraxial morphine.<sup>[10-12]</sup> Recent closed-claims data found that 13 of 93 claims made between 1995 and 2007 were due to respiratory depression; six cases involved intravenous opioids, three cases involved neuraxial opioids, and in the remaining four cases the drug and route were not named. The majority

of these cases resulted in significant morbidity or permanent brain damage, and resulted in treatment costs of approximate £2.75million.<sup>[13]</sup> Although the absolute risk of respiratory depression is small, concern for this adverse effect may result in underuse of neuraxial morphine for routine postoperative analgesia.<sup>[14]</sup>

This article reviews relevant publications addressing the issue of respiratory depression secondary to neuraxial morphine. A literature review of studies that examined neuraxial morphine-induced respiratory depression was performed. Published articles written in English between 1945 and 2010 were identified using the MEDLINE, Cochrane, EMBASE and Web of Science databases. Literature written in English using the terms 'intrathecal or spinal or neuraxial or extradural or epidural or neuraxial' and 'opioid', were combined with 'respiratory depression or respiratory failure'. 360 articles were reviewed by hand, of which 165 were excluded. We selected 63 articles containing 'opioids and neuraxial' and 132 articles containing 'morphine and neuraxial'. Additional articles were reviewed to explain certain points.

## 2. Pathophysiology of Respiratory Depression

Respiratory depression has been reported following both intrathecal and epidural morphine.<sup>[15,16]</sup> Respiratory depression following epidural morphine is classically described as biphasic,<sup>[17]</sup> with early (<2 hours) and delayed (>2 hours) presentations. Most reports of early respiratory depression involve lipophilic opioids (sufentanil or fentanyl) administered via the epidural route.<sup>[18-22]</sup>

Delayed respiratory depression is a phenomenon associated with hydrophilic morphine rather than lipophilic neuraxial opioids.<sup>[15,16]</sup> It usually

occurs 6–12 hours following intrathecal or epidural administration and may persist up to 24 hours.<sup>[17,23,24]</sup> Delayed respiratory depression is caused by rostral spread in the cerebrospinal fluid (CSF) and slow penetration into the brainstem. High concentrations of  $\mu$ -opioid receptors exist within the ventral medulla, which are important in the normal regulation of respiration. Direct application of small doses of opioid to the chemosensitive anterolateral surface of the medulla,<sup>[25,26]</sup> fourth or lateral ventricles,<sup>[27,28]</sup> or pontine or medullary respiratory centres can induce significant respiratory depression.<sup>[29]</sup> Respiratory depression was previously thought to result from the interaction of opioid in the CSF with ventral medullary opioid receptors.<sup>[30]</sup> Studies in rats suggested that respiratory depression occurring after the administration of opioids resulted from a dual effect involving  $\mu$ - and  $\delta$ -receptors.<sup>[31]</sup> More recently, the preBötzing complex located in the medulla has been identified as the site responsible for the decrease in respiratory rate following systemic administration of opioids. Neurons in the preBötzing complex expressing neurokinin-1 receptors are selectively inhibited by opioids, and therefore are the mediators of opioid-induced respiratory depression.<sup>[32]</sup>

### 3. Pharmacokinetics of Neuraxial Morphine

Epidural, intrathecal and plasma pharmacokinetics of opioids are complex, vary between neuraxial compartments, and can even differ within the epidural space itself depending upon level of insertion. The bioavailability of opioids in the intrathecal and epidural compartments is determined primarily by the drug's hydrophobicity.<sup>[33]</sup> Hydrophilic morphine has a high CSF bioavailability, excellent spinal penetration, prolonged duration and less systemic absorption than lipophilic opioids. Morphine penetrates the spinal cord slowly, facilitating cephalad spread in the CSF. A poor correlation between the analgesic effect and plasma levels of morphine has been observed following epidural administration, suggesting a predominantly spinal effect.<sup>[34,35]</sup> Morphine levels within the CSF following intrathecal

morphine administration are approximately 3 times those in plasma. Supra-spinal redistribution of morphine through the CSF plays an important role in the generation of analgesia and CNS side effects.<sup>[36]</sup>

The long duration of action of morphine is due to the slow rate of clearance of the drug from the opioid receptors.<sup>[37,38]</sup> In addition, morphine is absorbed more slowly from the intrathecal space than following epidural or intramuscular administration, further prolonging its analgesic effect.<sup>[39]</sup>

Direct administration of morphine into the CSF is the most efficient method of delivering opioid to the spinal cord receptors. Appreciable cervical CSF concentrations occur 1–5 hours after lumbar intrathecal morphine administration. Morphine reaches the cisterna magna and fourth and lateral ventricles by 1–2 and 3–6 hours, respectively.<sup>[40]</sup> The hyperbaric form of morphine decreases cephalad diffusion and minimizes the central depressant effects of the drug.<sup>[41]</sup> It remains within the CSF for prolonged periods and slowly diffuses to the plasma compartment.<sup>[42]</sup> Morphine is not metabolized within the CNS, and therefore morphine-6-glucuronide cannot be detected in CSF following intrathecal administration.<sup>[43]</sup> Elimination is thought to be dependent on reabsorption via arachnoid granulations.<sup>[44]</sup> The terminal elimination half-life of morphine within the CSF is 2–4 hours, similar to that within plasma.<sup>[45,46]</sup>

Peak blood and CSF levels of morphine occur at 10–15 minutes and 1–4 hours, respectively, following epidural administration.<sup>[38,46–48]</sup> Approximately 3% of the epidural morphine dose crosses the dura to enter the CSF.<sup>[46,47]</sup> Epidural morphine administration produces blood concentrations similar to those seen following an equivalent intra-muscular dose.<sup>[49]</sup> Animal studies examining behavioural and toxicological effects have failed to demonstrate neurotoxicity secondary to long-term administration of epidural and intrathecal morphine.<sup>[50]</sup>

### 4. Patients at Risk of Respiratory Depression

There are a number of well described risk factors for developing respiratory depression after neuraxial morphine (table I).<sup>[15,51–60]</sup> In 2009, the

**Table I.** Risk factors for respiratory depression

Risk factor	References
<b>Pharmacological</b>	
High opioid doses	51
Hydrophilic opioids (morphine)	52
Repeated opioid administration	53
Concomitant administration of systemic opioids	15,52
Co-administration of sedatives	53
<b>Anaesthesia</b>	
General anaesthesia	
Thoracic epidurals	54
<b>Patient</b>	
Advanced age	15,55
Female	56
Co-existing cardiopulmonary disease	55
Opioid-naïve patient	55
Morbid obesity	55,57
Obstructive sleep apnoea	52
Genetic (OPRM1:c.118A > G polymorphism)	58
<b>Miscellaneous</b>	
Co-administration of magnesium	59
Increased intrathoracic pressure (controlled ventilation, coughing, vomiting)	
Non-obstetric population	60

American Society of Anesthesiologists published practice guidelines for the prevention, detection and management of respiratory depression associated with neuraxial opioid administration.<sup>[52]</sup> These guidelines suggest that a history and physical examination directed at identifying risk factors, in particular sleep apnoea, should be performed in all patients prior to administration of neuraxial opioids. Importantly, opioid-induced respiratory depression can still occur in healthy patients receiving neuraxial morphine without co-existing morbidity,<sup>[53]</sup> and clinicians must anticipate this rare but hazardous event.<sup>[53,61]</sup> Caution should be exercised when prescribing systemic opioids (intravenous or oral) in addition to neuraxial morphine as this can compound the potential for early or delayed respiratory depression.

## 5. Incidence of Respiratory Depression

Numerous publications including randomized controlled trials, case reports, prospective and

retrospective analyses of databases, surveys and meta-analyses have attempted to define the true incidence of respiratory depression associated with neuraxial morphine use. Disparity of definitions used for the diagnosis of respiratory depression precludes identification of the exact incidence of this rare event. Definitions have included respiratory rate, hypercarbia, low arterial oxygen saturation (SaO<sub>2</sub>), decreased level of consciousness, increased level of sedation, treatment with naloxone and decreased ventilator response to hypoxia or hypercarbia.<sup>[62]</sup> In addition, the incidence of respiratory depression following neuraxial morphine has been shown to be dose-dependent. Therefore, the reported incidence of respiratory depression from earlier studies using larger doses may not be relevant to current clinical practice which utilizes smaller neuraxial morphine doses.<sup>[15,63,64]</sup>

The incidences of respiratory depression determined from large retrospective and prospective database analyses are outlined in table II.<sup>[57,65-73]</sup> The incidence is 0.26–3% for intrathecal morphine in dose ranges of 0.15–0.8 mg, and 0–2.8% for epidural morphine administration with dose ranges of 2–5 mg. These incidences are similar to those reported by Etches et al.<sup>[64]</sup> in 1989 (0.09–3%). In their review, the authors commented that the true incidence was unknown due to the lack of well designed prospective studies at the time. More recently, two meta-analyses determined the incidence of respiratory depression in patients receiving low-dose (<0.2 and 0.2–0.3 mg) intrathecal morphine to be 0–1.2%.<sup>[51,74]</sup> Table III shows recent randomized controlled trials performed since 2000 not included in the two mentioned meta-analyses.<sup>[75-88]</sup> The incidence of respiratory depression in these studies ranges from 0% to 3.4% in the 985 patients receiving intrathecal morphine in dose ranges between 0.025 to 0.4 mg. Differences in the incidences among the studies may reflect different doses, additional analgesics utilized, different surgical populations, and various definitions used to define respiratory depression.

Studies indicate that the incidence of respiratory depression is not greater with neuraxial compared with systemic administration of morphine.<sup>[51,66,74,89]</sup>

**Table II.** Studies with incidence data for respiratory depression secondary to neuraxial morphine

Study (year)	Type of surgery	n	Design	Outcome measured	Route	Additional opioids?	Incidence (%)
Kato et al. (2008) <sup>[65]</sup>	CD	1915	Retrospective	Bradypnoea: RR $\leq$ 10 Severe RD: required use of naloxone	IT 0.15 mg	Yes	Bradypnoea: 0.26 Severe RD: 0.052
Shapiro et al. (2005) <sup>[66]</sup>	General	1524	Retrospective	RR <10	IV-PCA vs E 4 mg every 16–24 h $\times$ 3 vs IT 0.2 mg	No (first 24 h)	IV-PCA: 1.86 E: 0.59 IT: 0.69
Flisberg et al. (2003) <sup>[67]</sup>	General	2696	Prospective	RR <8	E 2–4 mg + PCEA vs IV-PCA	No	E group: 0.04 IV-PCA group: 1.2
Gwirtz et al. (1999) <sup>[68]</sup>	General	5969	Prospective	RR $\leq$ 8 or PaCO <sub>2</sub> >50 mmHg	IT 0.2–0.8 mg	Yes	3
Tsui et al. (1997) <sup>[69]</sup>	General	245	Prospective	RR <10 or SaO <sub>2</sub> <90% or PaCO <sub>2</sub> >7 kPa	E 3–6 mg + infusion	No	2.8
Rygnestad et al. (1997) <sup>[70]</sup>	General	2000	Prospective	RR <8	E bolus 2 mg with 0.05% bupivacaine + infusion	Yes	1.7
Abouleish et al. (1991) <sup>[57]</sup>	CD	856	Prospective	SaO <sub>2</sub> $\leq$ 85% or RR $\leq$ 10	IT 0.2 mg	Yes	0.9
Fuller et al. (1990) <sup>[71]</sup>	CD	4880	Retrospective	RR <10	E 2–5 mg	Yes	0.25
Leicht et al. (1986) <sup>[72]</sup>	CD	1000	Prospective	RR <10, poor depth of respirations, or signs of airway obstruction	E 5 mg		0.4
Kotelko et al. (1984) <sup>[73]</sup>	CD	276	Prospective	RR <10	E 5 mg	Yes	0

CD=caesarean delivery; E=epidural; IT=intrathecal; IV-PCA=intravenous patient-controlled analgesia; n=number of patients; PaCO<sub>2</sub>=partial pressure of arterial carbon dioxide; PCEA=patient-controlled epidural analgesia; RD=respiratory depression; RR=respiratory rate (breaths/min); SaO<sub>2</sub>=oxygen saturation.

Although earlier studies suggested that respiratory depression was greater with intrathecal morphine compared with epidural administration,<sup>[15,37]</sup> these differences may be attributed to the higher intrathecal morphine doses used in those studies. More recent studies indicate that epidural and intrathecal morphine appear to provide similar analgesia and adverse effects (such as sedation, pruritus, nausea and vomiting) when an equipotent analgesia conversion ratio of 20–30:1 is used.<sup>[84,90,91]</sup> One potential disadvantage of epidural administration of morphine is that inadvertent subdural or intrathecal administration with a dose intended for the epidural route can lead to profound sedation and respiratory depression, potentially requiring opioid reversal, intensive care monitoring and ventilatory support.<sup>[92]</sup>

## 6. Neuraxial Morphine 'Analgesic Ceiling', Dose-Response and Dose-Related Adverse Effects

The optimal neuraxial opioid dose is essentially a balance between the conflicting demands of providing optimal analgesia while minimizing dose-related adverse effects. Several studies have attempted to determine the optimal dose of intrathecal and epidural morphine for post-operative analgesia.

### 6.1 Intrathecal Morphine Doses

Due to the widespread use of neuraxial opioids in obstetric patients, intrathecal and epidural morphine have been extensively studied in this setting. Palmer et al.<sup>[93]</sup> compared the analgesic

**Table III.** Recent key randomized controlled trials with intrathecal morphine

Study (year)	Type of surgery	n	Outcome measured	Dose	Additional opioids?	Incidence (%)
Frassanito et al. (2010) <sup>[75]</sup>	TKA	52		IT 0.1 mg vs femoral nerve block	Yes	0
Duman et al. (2010) <sup>[76]</sup>	TURP	54	RR <10	IT 0.025–0.05 mg	No	0
Yamashita et al. (2009) <sup>[77]</sup>	TURP	20	RR <10	IT 0.05 mg	No	0
Draisci et al. (2009) <sup>[78]</sup>	CD	64		IT 0.15 mg + sufentanil 5 µg vs SC 10 mg + sufentanil 5 µg	Yes	0
Andrieu et al. (2009) <sup>[79]</sup>	Retropubic prostatectomy	50	RR <8 or SaO <sub>2</sub> <90% or PaO <sub>2</sub> >70 mmHg	IT 4 µg/kg; IT 1 µg/kg + clonidine; morphine PCA	Yes	0
Massicotte et al. (2009) <sup>[80]</sup>	TAH	40	RR <8	IT 0.15 mg + fentanyl vs GA	Yes	IT: 0 GA: 5
Ko et al. (2009) <sup>[81]</sup>	Donor right hepatectomy	40	RR <8 or PaCO <sub>2</sub> ≥70 mm Hg	IT 0.4 mg vs PCA	Yes	0
Gehling et al. (2009) <sup>[82]</sup>	Orthopaedics	188	RR ≤10	IT 0–0.2 mg	Yes	Placebo: 1.5 0.1 mg: 1.6 0.2 mg: 3.4
Ziegeler et al. (2008) <sup>[83]</sup>	PSF	52	Naloxone requirement	IT 0.4 mg vs placebo	Yes	0
Dualé et al. (2003) <sup>[84]</sup>	CD	53	Not disclosed	IT 0.075 vs epidural morphine 2 mg	Yes	0
Techanivate et al. (2003) <sup>[85]</sup>	Laminectomy	40		IT 0.3 mg vs placebo	Yes	0
Devys et al. (2003) <sup>[86]</sup>	Abdominal surgery	60	RR <10	IT 0–0.4 mg	Yes	0
Fournier et al. (2000) <sup>[87]</sup>	THA	40	RR <8	IT 0.16 mg vs nalbuphine	Yes	0
Culebras et al. (2000) <sup>[88]</sup>	CD	90	RR <10	IT 0.2 mg vs nalbuphine	Yes	0

**CD** = caesarean delivery; **GA** = general anaesthesia; **IT** = intrathecal; **n** = number of patients; **PaCO<sub>2</sub>** = partial pressure of arterial carbon dioxide; **PCA** = patient-controlled analgesia; **PSF** = posterior spinal fusion; **RR** = respiratory rate (breaths/min); **SaO<sub>2</sub>** = oxygen saturation; **SC** = subcutaneous; **TAH** = total abdominal hysterectomy; **THA** = total hip arthroplasty; **TKA** = total knee arthroplasty; **TURP** = transurethral resection of the prostate.

efficacy of increasing intrathecal morphine doses (0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4 and 0.5 mg) following caesarean delivery and found no significant analgesic benefit using doses greater than 0.075 mg. Another dose-response study of intrathecal morphine 0.05, 0.1 and 0.2 mg in the post-caesarean population observed that 0.1 and 0.2 mg provided comparable effective post-caesarean analgesia, while the 0.05 mg dose was less effective.<sup>[94]</sup> However, the incidence of adverse effects was greater with the 0.2 mg dose. Milner et al.<sup>[95]</sup> reported that intrathecal morphine 0.1 mg produced similar post-caesarean analgesia to that of 0.2 mg. There were no reports of respiratory depression, but the lower dose resulted in less nausea and vomiting. Similarly, Yang et al.<sup>[96]</sup> found that intrathecal morphine 0.1 mg compared with

0.25 mg, provided similar analgesia but with fewer adverse effects post-caesarean delivery. A post-caesarean analgesia study using a wide range of intrathecal morphine doses (0–0.2 mg), found that the dose that produced a 50% effective response (ED<sub>50</sub>) was 0.02 ± 0.05 mg; however, significant analgesic variability was noted.<sup>[97]</sup> A systematic review recommended 0.1 mg as the optimal intrathecal morphine dose for caesarean delivery analgesia.<sup>[4]</sup> The use of multimodal adjuvant analgesia including NSAIDs postoperatively may further reduce dose requirements. Cardoso et al.<sup>[98]</sup> found that 0.025 mg of intrathecal morphine when combined with systemic diclofenac was as effective as 0.05 or 0.1 mg.

A number of dose-response studies with intrathecal morphine have been conducted in non-obstetric surgical populations. Sarma and



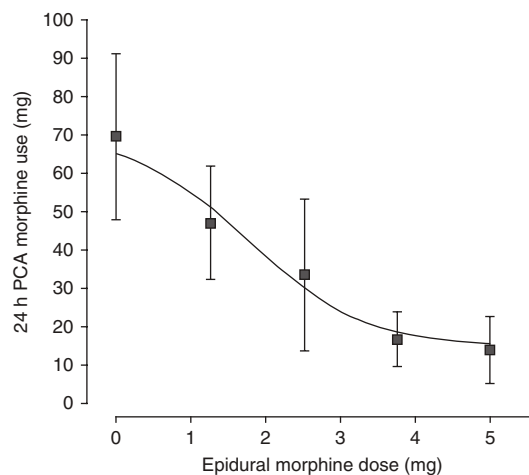
Bostrom<sup>[99]</sup> examined the dose-response of intrathecal morphine (0, 0.1, 0.3 and 0.5 mg) in patients undergoing total abdominal hysterectomy under general anaesthesia. The ‘analgesic ceiling’ in this study was 0.3 mg. Another dose-response study observed pain relief and adverse effects of intrathecal morphine doses (0, 0.04, 0.06, 0.08, 0.1, 0.12, 0.15 and 0.2 mg) in patients undergoing cholecystectomy with spinal anaesthesia.<sup>[100]</sup> Optimal analgesia without respiratory depression was obtained in the 0.06–0.12 mg dose range. The incidence of respiratory depression was greater with doses of 0.15 and 0.2 mg. Hassett et al.<sup>[101]</sup> examined the analgesic efficacy and adverse effect profile of 0.1, 0.2 and 0.3 mg intrathecal morphine in patients undergoing elective total knee replacement. They found morphine 0.2 mg to be the optimal analgesic dose, but observed no differences between adverse effects or respiratory depression amongst the doses studied. Slappendel et al.<sup>[102]</sup> studied various intrathecal morphine doses (0.025, 0.05, 0.1 or 0.2 mg) for total hip surgery and concluded that 0.1 mg was the optimal analgesic dose. The incidence of pruritus and requirement for antipruritic medication was dose-related, although there were no reports of respiratory depression or differences in oxygen desaturation among the different groups within this study. In a study of patients undergoing lumbar fusion randomized to receive morphine (0.2, 0.3 or 0.4 mg) injected into the dural sac under direct visualization, pain scores were better with 0.3 and 0.4 mg doses.<sup>[103]</sup> However, respiratory rate was lower and the partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) was consistently higher in patients receiving the 0.4 mg dose.

The effects of increasing intrathecal morphine doses (0.2, 0.4 and 0.6 mg) were assessed in non-surgical healthy, young, adult male volunteers.<sup>[23]</sup> The authors reported dose-related respiratory depression with significant decreases in SpO<sub>2</sub> (measured by pulse oximetry), the need for supplemental oxygen, and increased peak mean PaCO<sub>2</sub>. The PaCO<sub>2</sub> peaks occurred 6.5–7.5 hours after intrathecal morphine administration. A meta-analysis of 28 studies (n=790) determined adverse effects of intrathecal morphine in patients undergoing surgery with spinal anaesthesia.<sup>[51]</sup>

The authors found that intrathecal morphine resulted in an increased incidence of adverse effects (pruritus, nausea and vomiting) compared with patients not receiving intrathecal morphine. The incidence of pruritus was found to be dose-dependent. Higher doses ( $\geq 0.3$  mg) of intrathecal morphine were associated with a greater number of episodes of respiratory depression, 9% (7/80) compared with lower doses 1% (2/247), but the difference in incidence was not statistically significant.

### 6.2 Epidural Morphine Doses

The dose-effect relationship of epidural morphine has also been studied. A dose-response study by Palmer et al.<sup>[104]</sup> determined that the optimal post-caesarean analgesic dose of epidural morphine was 3.75 mg. In the dose range studied (0, 1.25, 2.5, 3.75 and 5 mg), increasing the dose beyond this ‘analgesic ceiling’ did not improve post-operative analgesia or reduce opioid use (figure 1). A 3 mg dose of epidural morphine was similarly recommended by Fuller et al.<sup>[71]</sup> based on a large retrospective post-caesarean study. Chumpathong et al.<sup>[105]</sup> found similar post-caesarean analgesia and adverse effects with 2.5, 3 and 4 mg doses of epidural morphine. A study by Rosen et al.<sup>[106]</sup> demonstrated that 2 mg did not provide adequate post-caesarean analgesia compared with 5 and 7.5 mg of epidural morphine.



**Fig. 1.** Dose-response relationship of intrathecal morphine for post-caesarean analgesia. PCA = patient-controlled analgesia [reproduced from Palmer et al.<sup>[104]</sup> with permission].

The analgesic and adverse effects of 1, 2, 3, 4 and 5 mg epidural morphine were examined in patients undergoing orthopaedic procedures.<sup>[107]</sup> Authors recommended 3 mg of epidural morphine as the optimal dose. Patients receiving  $\geq 2$  mg required less postoperative analgesia and experienced less postoperative pain, but the 5 mg dose produced mild respiratory depression (mean PaCO<sub>2</sub> 5 mm Hg greater than control group). A dose-dependent increase in pruritus and urinary catheterization was also observed. Rawal and Wattwil<sup>[63]</sup> performed a dose-response study in healthy volunteers administering epidural morphine doses of 2, 4 or 10 mg, and in the clinical part of the study administering epidural morphine 4 mg in surgical patients undergoing cholecystectomy. The authors found a dose-related depression in ventilatory drive (reduction in minute ventilation and increase in partial pressure of end tidal carbon dioxide [PETCO<sub>2</sub>]) in the healthy volunteers. PETCO<sub>2</sub> levels were higher and remained elevated longer in surgical patients than in volunteers given the same 4 mg dose. An infusion of naloxone (5  $\mu$ g/kg/hour) was also found to prevent respiratory depression in the volunteers.

### 6.3 Optimal Intrathecal and Epidural Morphine Dose Recommendations in the Surgical Setting

Dose-response studies show that neuraxial morphine appears to have an analgesic efficacy 'ceiling'. The optimal 'single-shot' intrathecal dose appears to be 0.075–0.15 mg and the ideal 'single-shot' epidural morphine dose is 2.5–3.75 mg. Analgesic efficacy studies have not been adequately powered to show differences in the incidence of clinically significant respiratory depression. However, opioid-related adverse effects, particularly pruritus, have been found to be dose-related in a number of studies.

## 7. Drugs to Minimize Opioid-Related Respiratory Depression

Opioid antagonists such as naloxone are available clinically to treat opioid-induced respiratory depression.<sup>[108]</sup> However, their use may

lead to a loss in analgesia resulting in difficult pain management.<sup>[109]</sup> Moreover, the potential for re-narcotization exists due to the relatively short elimination half-life of naloxone. A number of adverse effects secondary to reversal of analgesia and release of catecholamines by a central mechanism have been described following the use of opioid antagonists such as naloxone. These adverse effects include pain, psychological stimulation, and sympathomimetic responses including pulmonary oedema in severe circumstances.<sup>[110]</sup> A continuous naloxone infusion of 3–4  $\mu$ g/kg/hour for up to 10 hours has been recommended by some to avoid such adverse effects,<sup>[111]</sup> whereas others recommend naloxone infusions with intermittent supplemental dose titration with repeated small boluses of 0.8  $\mu$ g/kg until adequate reversal of respiratory depression is achieved.<sup>[112]</sup>

There is much interest in developing therapeutic interventions that reverse respiratory depression secondary to opioids whilst preserving their analgesic effects. Researchers have recently focused on using non-opioid drugs such as serotonin receptor agonists, ampakines ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid [AMPA] receptor modulators) and minocycline. A number of studies examining these newer drugs have proven effective in animal models;<sup>[113,114]</sup> however, few have thus far shown to be clinically beneficial. Glutamate-mediated neurotransmission via AMPA receptors at the preBötzing complex is crucial part of the generation of rhythmic respiratory pattern.<sup>[115-117]</sup> In 2010, Oertel et al.<sup>[118]</sup> studied ampakine CX717 in 16 healthy male volunteers in whom intravenous alfentanil at a target concentration of 100 ng/mL was used to induce respiratory depression. A decrease in respiratory rate was noted to be  $3 \pm 33\%$  in those receiving a 1.5 g oral dose of CX717 prior to the alfentanil compared with  $26 \pm 28\%$  in the placebo group receiving no ampakine. Ventilator response to hypercapnic challenge and blood oxygenation were also shown to be less significantly affected with CX717 compared with the placebo group. Importantly, the authors observed that the analgesic effects of alfentanil were unchanged by the CX717. The mechanism of action is thought to be an AMPA receptor neuronal excitation by



the CX717, which counteracts the depression caused by the  $\mu$ -opioid receptors at the pre-Bötzing complex.<sup>[119]</sup> Although early in its development, there is considerable potential for the use of this drug in patients receiving neuraxial morphine.

Repinotan is a selective serotonin (5HT)<sub>1A</sub> receptor agonist, which has been investigated in humans for its neuroprotective effects following stroke<sup>[120]</sup> and traumatic brain injury.<sup>[121]</sup> Guenther and colleagues<sup>[122]</sup> demonstrated spontaneous breathing in anaesthetized rats following morphine-induced respiratory depression. The dose-response curve of spontaneous breathing following morphine-induced ventilatory depression appears to be 'bell shaped' after 5HT<sub>1A</sub> receptor stimulation, which suggests diminished stimulatory effects at higher concentrations.<sup>[123]</sup> The effects on opioid-induced respiratory depression and nociception are yet to be established in humans.

Microglial inhibitors have shown potential to enhance the analgesic efficacy of morphine. Minocycline, a tetracycline derivative and microglial inhibitor,<sup>[124]</sup> improved analgesia and reduced opioid-induced respiratory depression in rats.<sup>[114]</sup> These findings may stimulate future research of this drug in a clinical setting. Sodium/proton exchanger type 3 (NHE3) inhibitors that act centrally on respiratory pathways are another class of drugs that warrant further study.<sup>[125,126]</sup>

## 8. Conclusion

Neuraxial morphine has contributed significantly to improve analgesia in many surgical settings. The analgesic benefits related to neuraxial morphine administration far outweigh the risks associated with the rare incidence of respiratory depression. In addition, the risk of respiratory depression following neuraxial morphine is not greater than that following systemic morphine administration.<sup>[66,89]</sup> Neuraxial morphine appears to have an analgesic efficacy 'ceiling' and utilizing larger doses may increase adverse effects without necessarily improving analgesia. The optimal intrathecal dose appears to be 0.075–0.15 mg and the ideal epidural morphine dose is 2.5–3.75 mg. There are a number of novel non-

opioid drugs such as serotonin receptor agonists, ampakines and minocycline being developed that may reduce the risk of opioid-induced respiratory depression in the future.

## Acknowledgements

No sources of funding were used in the preparation of this review. Brendan Carvalho reports receiving funding from EKR Therapeutics as principal investigator for study conduct (DepoDur™), and Epimed International, Inc. for research efforts. Drs Sultan and Gutierrez report no conflicts of interest that are directly relevant to the content of this review.

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