Review Article

Respiratory depression and spinal opioids

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Key words

ANAESTHETIC TECHNIQUES: epidural, spinal, narcotics;
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Administration of epidural and intrathecal opioids may provide excellent postoperative analgesia, but a minority of patients will suffer dangerous respiratory depression. This review discusses the detection and measurement of respiratory depression and summarizes the relevant literature as it pertains to epidural and intrathecal opioid administration. The respiratory depressant effects and pharmacokinetics of spinal opioids are reviewed. The clinical implications and areas of future investigation are discussed.

Introduction

Historical perspective

With the discovery by Pert and Snyder¹ in 1973 of specific opioid receptors and their subsequent identification in the substantia gelatinosa of the spinal cord²⁻⁴ the stage was set for the clinical application of opioids to the sub-arachnoid and epidural spaces. This was first reported in 1979 when Wang *et al.*⁵ published a controlled study of the use of intrathecal morphine in cancer patients which demonstrated the remarkable analgesic properties and prolonged duration of action of the drug. One month later Behar, Olshwang *et al.*⁶ published their series of ten patients given epidural morphine. The same year Cousins *et al.*⁷ reported the successful use of epidural meperidine and demonstrated that analgesia correlated with CSF but not serum concentrations of the drug. These authors also coined the term "selective spinal analgesia" which refers to the presence of analgesia without motor, sensory, or autonomic deficits. These initial clinical studies proved a potent stimulus to further research, and since their publication there has been a remarkable proliferation of case reports and clinical trials, as well as several reviews of the basic pharmacology⁸⁻¹² and clinical application.¹³⁻¹⁶

Advantages of spinal opioids

The potential advantages of spinal opioids were immediately apparent. They appeared to provide excellent analgesia without any demonstrable motor, sensory, or autonomic deficits.⁵⁻⁷ In addition, animal studies² and these initial clinical studies suggested that cephalad flow

of opioid via the cerebral spinal fluid was unlikely to occur. If this was true, then the central nervous system side effects of opioids such as respiratory depression, sedation, and nausea and vomiting should be minimal. (Two of the patients described by Cousins *et al.*⁷ received naloxone 0.4 mg for "mild sedation".)

Disadvantages of spinal opioids

In June of 1979, only four months following the initial report of Wang *et al.*,⁷ Scott and McClure¹⁷ reported two patients who developed severe respiratory depression 30 minutes following epidural meperidine. Other similar reports soon followed.¹⁸⁻²¹ These reports were particularly disturbing because respiratory depression was delayed up to 11 hours following administration of the drugs, and appeared after as little as one milligram of intrathecal morphine, and in the absence of any other narcotic administration.^{20,21}

Since 1980, much information has accumulated concerning spinal opioids, and two facts stand out. The first is that they often provide excellent analgesia. The second is that respiratory depression, and in particular delayed respiratory depression, continues to be a problem in a manner that is not entirely predictable.

Purpose of this review

This paper reviews the problem of respiratory depression associated with epidural and intrathecal opioids. The problems of defining and detecting respiratory depression in the clinical setting are discussed. Relevant clinical studies and case reports are summarized and critically reviewed. Proposed mechanisms of early and late respiratory depression are reviewed and the clinical implications are discussed.

Respiratory depression

Definition

From a pathophysiologic point of view, respiration is depressed if the subject fails to respond adequately, on a moment-to-moment basis, to hypercapnia or hypoxia. Central respiratory depression, the focus of this review, exists when the respiratory neurons of the medulla fail to respond appropriately to these stimuli.²² With this definition in mind, it is apparent from the discussion which follows that no single measurement technique can adequately assess the degree of respiratory depression.

Detection and measurement

The detection and measurement of drug-induced respiratory depression is reviewed by Jordan,²³ who emphasizes that the methods used, "must be able not only to quantify

TABLE 1 Methods of detection and measurement of respiratory depression (adapted from Jordan (1982)²³)

Measurement of resting breathing

Ventilation

- Indirect
 - Canopy
 - Strain gauge
 - Respiratory inductive plethysmography
- Direct

- Spirometry
- Pneumotachograph

Blood-gas tensions

- Direct
 - Arterial blood gases
- Indirect
 - Transcutaneous PO₂ or PCO₂
 - End-tidal CO₂
 - Oximetry

Tests of chemosensitivity

Response to hypercapnia

- CO₂ response curve
- Mouth occlusion pressure

Response to hypoxia

Measurement of response to added mechanical load

the degree of respiratory depression, but also to detect alterations in the regulation of breathing which may indicate the potential for serious depression to occur." Methods currently available are summarized in Table 1.

In the clinical setting, and in particular with spontaneously breathing patients after surgery, monitoring should be continuous, non-invasive, and comfortable. It should not require any active patient cooperation.²³ The techniques used should detect transient events including hypoxaemia, apnoea and periods of severe hypoventilation, and should discriminate between central and obstructive apnoea. Of the available methods, indirect measurement of ventilation and blood gas tensions, in combination, come closest to meeting these criteria.

INDIRECT METHODS

Measurement of ventilation

Strain gauges placed around the chest and abdomen vary in electrical resistance as circumference varies. Although ventilation may be measured using this technique, results may be inaccurate because of the variable relationship between circumference and volume which occurs with changes in posture or at the extremes of lung volumes.^{23,24}

Respiratory inductance plethysmography, in which two zig-zag coils of wire are placed around the chest and

abdomen, does give a semi-quantitative measurement of ventilation which is less sensitive to changes in posture. The device is comfortable and therefore well suited for continuous monitoring. In addition, it allows the observer to discriminate between obstructive and central apnoeas. However, this technique does not detect hypoxaemia or hypercapnia directly.^{23,25-28}

The transcutaneous carbon dioxide electrode requires the skin to be heated, recalibration due to electrode drift, and may not reflect the arterial PCO₂ accurately. Because of these and other problems it has not achieved popularity. The measurement of PETCO₂ via nasal cannulae is currently the most practical technique for the indirect measurement of arterial carbon dioxide tension. The PETCO₂ is measured on a breath-by-breath basis. However, this may be inaccurate if the sampling catheter is occluded by water or secretions, if the sampled gas is not true PETCO₂, or if significant ventilation-perfusion mismatching occurs. Even a properly functioning system may fail to indicate brief periods of severe hypoventilation.²⁹

In the clinical setting it is most common to measure the respiratory rate intermittently. While this is clearly the simplest form of monitoring, there are serious shortcomings. The technique does not detect transient events. In addition, the relationship between respiratory rate, arterial PCO₂, and hypoxaemia is unreliable. In particular, patients may be hypoxaemic and hypercapnic yet have a normal respiratory rate.³⁰⁻³²

Measurement of oxygenation

The best indirect measurement of arterial PO₂ is obtained with the pulse oximeter. Oximeters are generally accurate at saturations above 70 per cent, have a rapid response time, and are comfortable for long-term monitoring. In the presence of supplemental oxygen, however, saturation may be well maintained despite significant hypoventilation or apnoeic episodes. Transcutaneous measurement of PO₂ is dependent upon tissue perfusion and has a slow response time. It has been replaced largely by pulse oximetry.

DIRECT MEASUREMENT

Measurement of ventilation

Direct measurement of minute ventilation by mask, mouthpiece, or canopy monitor is not a sensitive measure of respiratory depression in the postoperative patient. A mouthpiece and nose clip or tight-fitting mask preclude extended periods of monitoring in the resting patient, and may alter the pattern of breathing.^{23,33} Nor do these techniques detect hypoxoemia or altered chemosensitivity,

both of which are frequent in the postoperative patient.³⁴⁻³⁶

Canopy monitors, which enclose the patient's head in a rigid, clear plastic box with a seal around the neck, allow continuous, quantitative monitoring of tidal volume, minute ventilation, and metabolic rate.²⁹ However, the patient must remain supine, hypoxaemia is not detected, and it is not possible to discriminate between obstructive and central apnoea.

Measurement of chemosensitivity

Altered chemosensitivity, in particular the depression of the CO₂ response curve, is considered a sensitive index of respiratory depression.^{23,36,37} Subjects should serve as their own controls because there is significant between-subject variability. Calculation of the CO₂ response curve is time-consuming and requires patient cooperation. It has not been determined whether an altered CO₂ response curve is a reliable predictor of transient apnoea or hypoventilation, therefore it is not proper to conclude that a normal curve in an awake patient implies normal respiratory control during rest or sleep. Similar criticisms apply to the measurement of mouth occlusion pressure and the response to added mechanical loads.

The response to hypoxia has also been measured, but it too requires some degree of patient cooperation. In addition, ethical constraints restrict the use of this technique in the clinical setting.^{34,36,37}

Pre-existing respiratory abnormalities

SLEEP

Depending upon the sensitivity of the techniques applied and the criteria used, sleep-related breathing disorders may be diagnosed in 44 to 82 per cent of otherwise healthy older subjects.³⁸ These problems include hypoventilation, apnoeic episodes, and arterial oxygen desaturation.³⁹⁻⁴¹ Other normal physiological changes associated with sleep are summarized in Table II.⁴²⁻⁴⁷

PRE-EXISTING DISEASE

Many factors may increase the frequency and/or duration of respiratory abnormalities during sleep. These include obesity,^{41,48} anatomical changes associated with increased upper airways resistance,⁴⁹⁻⁵⁴ various neurologic disorders,⁵⁵ and left ventricular failure.^{42,56,57}

It is uncertain whether chronic obstructive lung disease is associated with a greater frequency of apnoeic episodes or hypoventilation.^{58,59} However, numerous studies have demonstrated more frequent episodes of significant hypoxaemia.⁵⁸⁻⁶⁴ This has been attributed in part to a lower baseline arterial PO₂.

TABLE II Normal respiratory physiological changes during sleep (references as per text)

Decreased minute ventilation, primarily due to decreased tidal volume.
PaCO ₂ increased 3–7 mmHg.
PaO ₂ decreased 4–9 mmHg.
Decreased response to CO ₂ .
Decreased response to hypoxia.
Periodic breathing or apnoeic episodes.
Decreased upper airway muscle tone, with increased airways resistance.
Decreased intercostal muscle activity during REM sleep, therefore increased diaphragmatic breathing.
Decreased FRC.

POSTOPERATIVE RESPIRATORY CHANGES

After surgery several factors combine to impair both the mechanical aspects and the control of breathing.⁶⁵ Although functional residual capacity (FRC) is decreased during surgery, it appears to recover in the first few postoperative hours. However, following upper abdominal or thoracic surgery, FRC is decreased by approximately 30 per cent at 24 hours and may take a week or more to recover. This is associated with ventilation/perfusion mismatching and airway closure with the resultant increase in shunt fraction and decrease in arterial oxygen tension. Following upper abdominal surgery this decrease is typically about twenty mmHg.⁶⁶ It is important to note that in the presence of a low PaO₂ and decreased FRC even a brief period of apnoea or hypoventilation may result in severe hypoxaemia.^{56,67}

Control of ventilation is also altered in the immediate postoperative period. The responses to both hypoxia and hypercapnia are greatly diminished at low concentrations (0.1 MAC) of volatile agents.^{34,68} This is of particular significance in the recovery room. Thus, it is apparent that the postoperative patient may be particularly vulnerable to the depressant effects of narcotics.

Of particular importance is the apparently synergistic effect on the CO₂ response curve of parenteral morphine in the sleeping subject.⁴⁷ In volunteers, both sleep and morphine shift the curve down and to the right, but the effect of both together may be more than additive. This synergism adds to the difficulty of extrapolating from awake to sleeping patients when studying the regulation of respiration. As a further illustration, Catley *et al.*³⁰ compared intravenous morphine infusion with regional analgesia in postoperative patients who had undergone either cholecystectomy or total hip replacement. No patient receiving regional analgesia had any episodes of severe oxygen desaturation (<80 per cent). In contrast, 10 of 16 patients receiving intravenous morphine had frequent episodes of desaturation. In addition, all episodes of desaturation occurred during sleep.

Review of clinical studies and case reports

Morphine

CASE REPORTS

Intrathecal

There are numerous case reports of delayed respiratory depression following intrathecal morphine, and although the circumstances vary, most ascribe the response to a relative overdose (3–20 mg) either by design,^{18,19,69,70} drug error,^{71,72} or intrathecal migration of an epidural catheter.⁷³ In general, respiratory depression became apparent at 4–12 hours post-injection, but it is important to note that one patient given 3 mg of intrathecal morphine became apnoeic following the administration of parenteral narcotics 21 hours after the epidural dose.⁶⁹ Most patients responded immediately to naloxone, but frequently needed repeated doses or an infusion.

A case report by Davies *et al.*²¹ merits special consideration. Three of six patients given 1 mg of intrathecal morphine at the time of routine spinal anaesthesia developed severe delayed respiratory depression. These patients are noteworthy because of the small dose given, the absence of any parenteral narcotics, and age. One of the patients was a 20-year-old healthy male who was "found comatose and apnoeic" ten hours following his surgery. Another patient, a 77-year-old female, was found comatose with a respiratory rate of two breaths per minute, nine hours after injection. She was treated with naloxone, but had three subsequent respiratory arrests at 12, 15, and 23 hours. Acute respiratory failure with secondary cyanosis and hypotension has also been reported following 0.4 mg of intrathecal morphine administered to a 74-year-old female.⁷⁴ These patients demonstrate that youth, a small dose, and the absence of parenteral narcotics do not reliably prevent life-threatening respiratory depression.

Epidural

Although epidural morphine is in widespread use, there are few reports describing respiratory depression. Respiratory depression has been associated with inadvertent overdose,⁷⁵ advanced age,^{76–78} co-existing administration of parenteral narcotics,^{77,79} and pre-existing disease.⁸⁰ In addition, there are several reports of significant respiratory depression in the absence of any suspected risk factors.

Reiz and Westberg⁸¹ reported one patient of 1200 who developed severe respiratory depression four hours following a second dose of 2 mg of epidural morphine. The patient's age was not stated, but no other potential risk

factors were noted. Jyu and Lamb⁸² reported severe respiratory depression in a healthy 49-year-old male given 2.5 mg of epidural morphine at the time of operation. This occurred five hours following injection, and six to seven hours following fentanyl 300 µg IV. The degree to which the fentanyl contributed to the problem is uncertain. London⁸³ found severe bradypnea 2.5–3 hours following epidural morphine 5 mg in a healthy 24-year-old female with no potential risk factors. Krane⁸⁴ reports severe respiratory depression in a 2½-year-old boy undergoing hypospadias repair. The child was healthy and received no other narcotics. However, 3.5 hours after epidural morphine 0.1 mg·kg⁻¹ the patient became unrousable and cyanotic with shallow respirations at a rate of 15·min⁻¹. This child required multiple doses of naloxone and a continuous naloxone infusion for several hours. These cases illustrate that life-threatening, delayed respiratory depression can occur in the absence of any known or suspected risk factors.

DIRECT MEASUREMENT

Intrathecal

The authors could find only one study which assessed chemosensitivity following intrathecal morphine. Ab-boud *et al.*⁸⁵ studied 33 healthy women undergoing Caesarean section with spinal anaesthesia. Patients were given either subarachnoid morphine 0.1 or 0.25 mg, or placebo. The CO₂ response curves were measured immediately after surgery and at 3, 6, 12, 16, and 24 hours later. There were no significant changes in the CO₂ response curves of patients who received subarachnoid morphine. This was in contrast to the patients given placebo followed by subcutaneous morphine in whom the CO₂ response curves were depressed at 1.5 and 3 hours after surgery.

Epidural

Several studies have directly assessed CO₂ sensitivity and ventilatory responses to epidural morphine in both volunteers and patients. However, small sample sizes and very different study designs make interpretation of the data difficult.

There is general agreement that epidural morphine causes early respiratory depression (one to six hours after the dose) comparable to or greater than a similar parenteral dose.^{86–92} This is manifested as an increase in PETCO_2 , a decrease in the slope of the CO₂ response curve, a decrease in the airway occlusion–pressure response, or a decrease in minute ventilation in response to a PETCO_2 of 55 mmHg.

There are relatively few studies which consider the

effects of epidural morphine on ventilatory control during the later phase of analgesia. Knill *et al.*⁸⁷ administered 3.5 or 7.0 mg of morphine either subcutaneously or epidurally to four volunteers. Subcutaneous morphine had minimal effects. However, following epidural morphine, the slope of the CO₂ response curve and minute ventilation were maximally depressed at six hours. The two subjects who received 3.5 mg of epidural morphine were retested at 24 hours at which time the CO₂ response curve was still mildly depressed and the PETCO_2 was still mildly elevated. However, given the large day-to-day variability of the CO₂ response curve, it is not possible to make any firm conclusions on the basis of these findings. Other studies have both supported^{86,90} and refuted^{92,93} them.

In a more recent study Rawal and Wattwil⁹¹ studied the effects on ventilatory control of 2, 4, or 10 mg of epidural morphine given to volunteers. With doses of 2 or 4 mg the results were similar. As measured by PETCO_2 , minute ventilation, and the response to four per cent CO₂ rebreathing, significant respiratory depression was present only after five hours. The situation for 10 mg of epidural morphine was very different. Respiratory depression was evident at one hour after injection and persisted for the duration of the study, 22 hours. The PETCO_2 was increased by 10–15 per cent on room air and during four per cent CO₂ rebreathing. Minute ventilation was decreased 35–40 per cent at one hour, and approximately 20–30 per cent for the duration of the study. The slope of the CO₂ response curve was decreased throughout the study period, but this was only significant at 8 and 13 hours. Rawal and Wattwil applied a similar protocol to ten patients after cholecystectomy given 4 mg of epidural morphine. Significant respiratory depression was found at five and ten hours but did not persist.

Several of the papers cited above also assessed changes in tidal volume and respiratory rate. Kafer *et al.*⁹² found that the slopes of both the tidal volume vs CO₂ and the rate vs CO₂ response curves were decreased but the change in rate was attenuated to a greater degree than the change in volume (i.e., rate decreased more than volume). This is in contrast to the results of others^{90,91,93} who found that the decrease in minute ventilation at rest or during a CO₂ challenge was due primarily to a decrease in tidal volume. In particular, Rawal and Wattwil⁹¹ found that patients given epidural morphine after cholecystectomy had respiratory rates greater than control despite the presence of significant respiratory depression. These studies underscore the hazard of monitoring respiratory rate as the sole indicator of respiratory depression following epidural morphine.

Following parenteral narcotics the ventilatory response

to hypoxia is significantly decreased and approximately parallels the changes in the response to CO_2 .^{94,95} This has not been investigated in the context of epidural narcotics, but it seems probable that the response would be similar.

INDIRECT MEASUREMENT

Intrathecal morphine

Although small doses of intrathecal morphine may provide profound postoperative analgesia of long duration, this route of administration is less popular than epidural morphine for two reasons. First, with the exception of the rare patient who has an indwelling subarachnoid catheter it is impractical to give repeated doses. Second, the incidence of late respiratory depression is felt to be more common than with the epidural route.

There are few prospective studies which have examined intrathecal morphine, and none have monitored patients continuously. Barron and Strong⁹⁶ found no respiratory depression following 2 mg of intrathecal morphine in 26 patients for total hip replacement or lumbar disc surgery. However, no definition of respiratory depression is given, and no blood-gas analyses were done.

Samii *et al.*⁹⁷ administered hyperbaric intrathecal morphine 0.02 or 0.2 $\text{mg} \cdot \text{kg}^{-1}$ to 60 postoperative patients and measured PetCO_2 in those with a respiratory rate less than ten or with "sedation." Sedation occurred in the majority of patients, but only two (in the high-dose group) had a decrease in respiratory rate and an increase in PetCO_2 . Although respiratory depression was not detected in the "low-dose" group, two points must be considered. First, Samii used a hyperbaric solution and kept his patients in a 40 degree head-up position overnight. This may limit rostral spread, and, in fact, the two patients who showed respiratory depression were placed in the horizontal position at 7 and 11 hours. Second, the patients were monitored intermittently rather than continuously, so transient hypoxia and/or hypercarbia could have been missed.

Gjessing and Tomlin⁹⁸ prospectively studied 32 patients having either a total hip replacement or a cholecystectomy. Patients were monitored in the recovery room and blood-gas analyses were done if there was "possible concern over respiration." Initially patients were given 2 mg of intrathecal morphine, but with this dose respiratory depression was the rule rather than the exception. For the patients undergoing total hip replacement, significant respiratory depression requiring naloxone was common down to a dose of 1 mg. Naloxone was not required in the six patients given 0.8 mg, but at least one patient had significant hypercapnia at 8–12 hours. The cholecystectomy patients were all premedicated with meperidine and

disyrazine (a tranquilizer), and 10 of 13 required 1.5–8 hours of postoperative ventilation. At least one of the five cholecystectomy patients given 0.8 mg of intrathecal morphine had moderate hypercapnia at 12–16 hours postoperatively.

Moore *et al.*⁹⁹ studied 20 patients given 2.5 mg intrathecal morphine in hyperbaric tetracaine and demonstrated an increase in PaCO_2 at 2–3.5 hours. Monitoring of the patients was not described beyond 3.5 hours, therefore no conclusions regarding late respiratory depression are possible.

Two large surveys have attempted to document the incidence and circumstances of respiratory depression associated with intrathecal morphine. Gustafsson *et al.*¹⁰⁰ asked that all patients requiring naloxone be reported, and found that 4–7 per cent of 90–150 patients treated with intrathecal morphine developed significant respiratory depression. (Much of this data is reported in the paper by Gjessing and Tomlin⁹⁸ cited above.) Because of the somewhat restrictive definition of respiratory depression, this survey may underestimate the true incidence of the problem. Rawal *et al.*¹⁰¹ reviewed approximately 1100 patients receiving intrathecal morphine and found an incidence of 0.36 per cent. This lower incidence in the more recent survey may be due mainly to the lower doses given (0.2–0.8 mg). However, despite these lower doses, respiratory depression was reported in three patients given 0.3 mg of intrathecal morphine. In these patients respiratory depression became evident at seven to nine hours. This study, too, may underestimate the degree of the problem because there was no uniform definition of respiratory depression and no uniformity of monitoring.

Epidural morphine

Many prospective studies of epidural morphine have failed to detect clinically significant respiratory depression. This is to be expected in view of the relatively low incidence of the problem, often coupled with small sample sizes and insensitive measurements. In the discussion that follows, only those studies which detected respiratory depression are included. Several smaller studies which have detected respiratory depression following epidural morphine are summarized in Table III and will not be discussed further.

Scheinin and Rosenberg¹⁰⁹ compared epidural morphine 2 or 4 mg with either epidural bupivacaine or parenteral narcotics following upper abdominal surgery. In this unblinded study, no clinically apparent respiratory depression was detected, but the PaCO_2 measured at four hours following anaesthesia was found to be elevated in 1–3/10 patients in each group. Neither respiratory rate nor blood gases were monitored beyond four hours.

Asantila¹¹⁰ compared thoracic epidural morphine 4–6

TABLE III Respiratory depression detected in prospective studies of epidural morphine

Reference	Incidence	Dose	Comments
Cambers <i>et al.</i> ¹⁰² (1981)	1/10	10 mg	Delayed emergence from anaesthesia. Naloxone 0.2 mg $\times$ 1.
Torda and Pybus ¹⁰³ (1981)	1/130	4 mg	Resp. depression 12 hours post-injection. Not responsive to naloxone. Aetiology unknown.
Modig and Paalzow ¹⁰⁴ for (1981)	1/42	5 mg + 5mg	T8 epidural abdominal aortic aneurysm. Resp. depression 6 hours following 2nd dose.
Weddell <i>et al.</i> ¹⁰⁵ (1981)	1/34	8.4 mg	70 female. Somnolent and respiratory rate of 6, 6 hours after injection. Naloxone $\times$ 4 doses at 6, 8, 10 and 12 h.
Klinck and Lindop ¹⁰⁶ (1982)	1/10	8 mg	71 fit male. Thoracic epidural. Slow respiratory rate at 8 and 14 hours. Responded to naloxone $\times$ 2 doses.
Martin <i>et al.</i> ¹⁰⁷ (1982)	1/12	8 mg	Respiratory rate of 8 and PCO ₂ of 49, 10 hours post-injection. Responded to naloxone 0.2 mg.
Ready <i>et al.</i> ¹⁰⁸ (1987)	2/66	4–5 mg	Respiratory rate <8 on one occasion. Patients in no distress. Time since injection not given.

mg with intercostal block or epidural bupivacaine in 51 patients undergoing thoracotomy. Patients received a narcotic premedication, fentanyl was given throughout the anaesthetic at a rate of 100 $\mu\text{g} \cdot \text{h}^{-1}$, and oxycodone was given postoperatively on a prn basis. Blood-gas analyses were done and respiratory rates were measured at 1, 3, and 24 hours postoperatively. The PaCO₂ tended to be increased in all groups for the first 24 hours postoperatively. However, differences between groups were minor.

In contrast, El Baz *et al.*¹¹¹ found severe respiratory depression (defined as loss of consciousness and a PaCO₂ of greater than 60 mmHg) in 8 of 30 patients given thoracic epidural morphine. Patients scheduled for elective thoracotomy received 5 mg of epidural morphine at the beginning of surgery; no other narcotics were administered. Repeat doses were given as required, and the average number of doses in the first 24 hours was four. One of these eight patients suffered acute respiratory failure after a single dose. It is difficult to reconcile the marked difference in the results of these two studies.

Allen *et al.*¹¹² studied 70 patients given either 0, 2.5, or 10 mg of epidural morphine for postoperative analgesia. These investigators found no differences in respiratory rate, but with a single blood-gas analysis done at ten hours postoperatively did find a higher PaCO₂ in the patients given 10 mg. Four of 17 patients in this latter group had arterial CO₂ tensions in the range of 50–54 mmHg, but none required treatment. This study too, is confounded by the use of parenteral narcotics on a prn basis during the study period.

Lanz *et al.*¹¹³ gave 0, 1, 2, 3, 4, or 5 mg of epidural morphine for postoperative analgesia and monitored respiratory rate hourly for 24 hours and in 27 of 139 patients performed blood-gas analyses at frequent inter-

vals for the first 12 hours postoperatively. Pentazocine was given on a prn basis postoperatively. No differences in respiratory rate were detected, but the PaCO₂ was elevated by approximately 5 mmHg in the 5 mg group compared with the controls from 2.5 to 12 hours postoperatively. Unfortunately, the pain scores in the control group were higher than the 5 mg group, and the doses of pentazocine were not documented.

The four studies cited above illustrate some of the problems which make any conclusions concerning the true incidence of respiratory depression difficult. Patients are generally monitored intermittently rather than continuously, pain scores may vary between groups, and the use of parenteral narcotics on a prn basis adds a major confounding variable.

Two recent studies have addressed specifically the problem of respiratory depression. Madsen *et al.*¹¹⁴ measured respiratory rate and PaCO₂ hourly for ten hours in 18 patients given either 8 mg of epidural morphine intraoperatively or postoperatively. Meperidine 0.3–0.5 mg was given at the time of extubation to the postoperative group, but no other parenteral narcotics were given. If analgesia was inadequate, epidural morphine 4 mg was given on demand, but only at intervals greater than 30 minutes. There were no significant differences between groups, but in both groups the PaCO₂ was maximally elevated at five to six hours postoperatively. Two of 18 patients had respiratory rates of 8 $\cdot \text{min}^{-1}$ at the tenth postoperative hour, but neither required treatment. The authors make the point that, in general, hypoventilation occurs on the basis of a decrease in tidal volume rather than rate. Although the authors have clearly demonstrated postoperative respiratory depression, the lack of a parenteral narcotic control group makes it impossible to attribute the results to the epidural narcotics *per se*. Other

contributing factors may include the respiratory changes associated with anaesthesia and upper abdominal surgery, postoperative pain, and the systemic absorption of epidural morphine, rather than cephalad spread via the CSF.

Sandler *et al.*¹¹⁵ studied respiratory depression in 13 patients after thoracotomy who received either repeated doses of epidural or intravenous morphine for postoperative analgesia. In this randomized, double-blind trial, patients were monitored continuously by a trained observer and respiratory inductive plethysmography for 24 hours. Patients also had blood-gas analyses done at 2, 6, 12, and 24 hours. Pain scores were similar in both groups. The investigators found that the PaCO_2 in the epidural group was elevated 2–12 hours postoperatively, whereas it was elevated only at two hours in the intravenous group. The respiratory rates were consistently lower in the epidural group. The most interesting results pertain to the use of continuous respiratory monitoring. In the intravenous group, only one of five patients had an episode of slow respiratory rate, and none had apnoeic episodes. In the epidural group, however, five of eight patients had episodes of slow respiratory rates and six of eight had apnoeic episodes. These apnoeic episodes occurred up to 27 hours after surgery, and, in one individual, up to 22 hours after the last dose of epidural morphine. All patients who demonstrated apnoea or hypoventilation had received at least 10 mg of epidural morphine. Pulse oximetry was not used in this study and patients received supplemental oxygen throughout. Whether transient episodes of hypoxaemia occurred is unknown.

Several studies and retrospective reviews which have gathered data on large numbers of patients are frequently cited as evidence of a low incidence of significant respiratory depression. These deserve further comment. Reiz and Westberg⁸¹ report only a single case of respiratory depression in 1200 patients following 2 mg of epidural morphine. However, no definition of respiratory depression was given, nor was the type of monitoring described. In addition, the dose of only 2 mg is smaller than the doses in common use today.

Stenseth *et al.*¹³¹ described their experience with 1085 patients given 4–6 mg of epidural morphine. The patients were subjected to a wide variety of surgical procedures and anaesthetic techniques with variable amounts of intraoperative intravenous narcotics. Respiratory depression was not defined, but was diagnosed clinically in 10/1085 patients. In nine of the ten patients, the diagnosis was made on the basis of a gradually decreasing respiratory rate; the one remaining patient had a normal rate but was excessively somnolent. Blood-gas analysis was done in only three of the ten patients. Seven of the ten patients received between 350 and 800 μg of fentanyl intraoperatively. With no control group, no standardized anaesthetic

technique, and no definition of respiratory depression or description of the monitoring techniques, it is difficult to draw any conclusions concerning the true incidence of respiratory depression.

Two nationwide retrospective surveys have been carried out in Sweden and have reviewed very large numbers of patients. Gustafsson *et al.*¹¹⁰ reported 23 cases (0.25–0.4 per cent) of respiratory depression requiring naloxone among 6000–9150 patients. (The numbers are inexact because they may be based on the estimated number of cases rather than comprehensive chart reviews.) Nineteen of the 22 also received parenteral opioids, ten were over 70 years of age, and ten received thoracic epidurals. In a second nationwide study, Rawal *et al.*¹⁰¹ claimed an incidence of 0.09 per cent in 14,000 patients. This pertains to delayed (3–12 hours) respiratory depression only, and excludes patients in whom respiratory depression was apparent within the first hour following the administration of the drug. Of these 13 patients, ten were 65 years of age or more, 11 were classified as ASA Status III–IV, and nine had a narcotic premedication. These two surveys suggest that the incidence of clinically apparent respiratory depression is much less than one per cent, and is rare in healthy, young patients who do not receive additional parenteral narcotics. The true incidence of clinically significant respiratory depression is still uncertain. These retrospective surveys are based on incomplete data, inconsistent criteria for significant respiratory depression, and unspecified monitoring techniques.

A less optimistic picture is provided by Mehnert *et al.*¹¹⁶ These investigators claimed that “hypoventilation” occurred in 8/268 patients, and that two of these eight required naloxone. Hypoventilation was not defined, and no patient characteristics were given, but patients were given 1–6 mg of epidural morphine. It is not certain from the text whether parenteral narcotics were given. Why these investigators found an incidence of 0.74 per cent and Rawal *et al.*¹⁰¹ (*vide supra*) found an incidence of 0.09 per cent is unclear.

Most recently, Ready *et al.*¹¹⁷ documented respiratory depression in 4/623 patients receiving epidural morphine. The patients ranged in age from 57–69, all had major abdominal surgery, and three of the four had intraoperative narcotics. Respiratory depression associated with marked sedation or unconsciousness occurred 2.75–13.5 hours postoperatively. These authors point out that there is a poor correlation between the degree of hypoventilation and the respiratory rate. One patient had a PaCO_2 of 95 mmHg despite a respiratory rate of 12 $\cdot \text{min}^{-1}$.

The use of epidural morphine to provide analgesia following Caesarean section deserves particular mention. Depressed CO_2 responsiveness may be present for up to

24 hours following the administration of epidural morphine 5 mg to patients after Caesarean section.¹¹⁸ However, the incidence of clinically significant respiratory depression appears to be very low.

Kotelko *et al.*¹¹⁹ gave a single dose of 5 mg of epidural morphine to 276 patients having Caesarean section under lumbar epidural anaesthetic. No patients developed a slow respiratory rate (less than $10 \cdot \text{min}^{-1}$), but one was given naloxone for somnolence. Writer *et al.*,¹²⁰ in a double-blind study, found no evidence of respiratory depression (not defined, but including clinically significant bradypnoea) in 28 patients after Caesarean section.

Leicht *et al.*¹²¹ studied 1000 patients prospectively who had been given epidural morphine 5 mg following Caesarean section. Respiratory depression was defined as a respiratory rate less than $10 \cdot \text{min}^{-1}$ and was diagnosed clinically in four of the 1000 patients. Two of these patients were observed and required no further treatment. One of the two who subsequently received naloxone had a respiratory rate of nine but had a normal blood-gas analysis. The one remaining patient had a respiratory rate of four to six and a PaCO_2 of 76 mmHg. The authors note that respiratory depression came on slowly in this patient, and if naloxone had been administered when the respiratory rate was nine to ten, the later, severe respiratory acidosis and hypoxia might have been avoided. It is unknown how many patients had significant CO_2 retention but normal respiratory rates.

McMorland and Douglas¹²² state that, in their institution, only two of 3000 patients have developed a slow respiratory rate following Caesarean section and epidural morphine, and in neither of these patients was there any suggestion of hypoxia or hypoventilation. Writer¹²³ confirms that the experience at his institution is similar. In each case cited above respiratory rate with or without somnolence was monitored intermittently, and periods of apnoea or hypoventilation may have occurred. Notwithstanding this criticism, the use of epidural morphine in this patient population has a remarkably safe record.

Fentanyl

CASE REPORTS

There is one report of life-threatening respiratory depression following epidural fentanyl.

Wells and Davies¹²⁴ reported a single patient who developed profound CNS depression, airway obstruction, and bradypnoea following epidural fentanyl 100 μg . The patient was an obese, diabetic male who had uneventful extra-corporeal shock wave lithotripsy (ESWL) with an L_{1-2} epidural and bupivacaine 0.5 per cent 3 mls and fentanyl. Following surgery the patient became progressively more somnolent and required several doses of

naloxone. The patient received small doses of midazolam, nalbuphine, and droperidol perioperatively, but remained cooperative throughout the procedure. The authors felt that the patient's narcotized state could not be explained on the basis of the parenteral drugs given, and there was no evidence of subarachnoid catheter migration. They speculated that the shock waves associated with ESWL may have contributed to rapid cephalad migration of the fentanyl in this obese patient. It is uncertain why symptoms developed in this patient but not in others given a similar anaesthetic.

DIRECT MEASUREMENT

Lam *et al.*¹²⁵ found no change in resting ventilation or the CO_2 response curve following epidural fentanyl 100 μg administered to healthy volunteers, but several subsequent studies have demonstrated respiratory depression. Negre *et al.*^{126,127} administered epidural fentanyl 200 μg to unpremedicated volunteers. These investigators found no change in minute ventilation or PETCO_2 , but did find a significant decrease in the CO_2 response curve from 30 to 120 minutes. No significant respiratory changes were detected in the control group given the same dose by intramuscular injection.

Renaud *et al.*¹²⁸ examined the respiratory effects of epidural fentanyl given as a $1 \mu\text{g} \cdot \text{kg}^{-1}$ loading dose followed by a $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion in eight patients after orthopaedic surgery. Analgesia was described as adequate in seven of the eight patients. None had "clinically significant respiratory depression." The mean PaCO_2 was mildly elevated during the 18-hour study period but this was not statistically significant. However, the CO_2 response curve was significantly depressed throughout. In a similar study, Ahuja and Strunin¹²⁹ gave epidural fentanyl $1.5 \mu\text{g} \cdot \text{kg}^{-1}$ followed one hour later by an infusion of fentanyl $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. These investigators found that PETCO_2 , measured continuously, increased slightly within 15 minutes of drug administration, and remained elevated for one hour before gradually returning to normal. Although the average increase in PETCO_2 was small and not significant, in two of 21 patients, it increased to approximately 60 mmHg within 30 minutes, and remained significantly elevated for 90 minutes. Over the eighteen hours of the study no late increases in PETCO_2 were detected.

INDIRECT MEASUREMENT

Several clinical reports support the impression that clinically significant respiratory depression is unusual following epidural fentanyl administration. MacKersie *et al.*¹³⁰ reported that ventilation improved in patients injured by blunt chest trauma after epidural fentanyl given as a 100 μg loading dose followed by a $50 \mu\text{g} \cdot \text{hr}^{-1}$

infusion. They reported that 85 per cent of patients had good to excellent analgesia with no change in PaCO_2 . In addition, maximum inspiratory force and FVC improved significantly. One patient had symptoms suggestive of "systemic narcosis," but no naloxone was required and the aetiology of the symptoms was uncertain.

Epidural fentanyl has also been reported to provide effective postoperative analgesia with no clinically significant respiratory depression following thoracic and abdominal surgery.^{131,132} Again, these clinical studies were neither blinded nor controlled, and respiratory depression was defined only in terms of respiratory rate or an obvious decrease in the level of consciousness.

Taken as a whole, the data concerning epidural fentanyl suggest that although respiratory depression as measured by depression of the CO_2 response curve is expected, clinically significant hypoventilation is unusual. It is apparent that a well designed, controlled, prospective study comparing epidural fentanyl, epidural morphine, and parenteral narcotics is required to resolve these issues.

Meperidine

There are several reports of early respiratory depression following epidural meperidine, but no well-documented reports of delayed respiratory depression, and there are no studies which measure the changes in the CO_2 response curve.

Scott and McClure¹⁷ reported two postoperative patients who had severe bradypnoea approximately 30 minutes following epidural meperidine 50–100 mg. Both these patients received a narcotic premedication four hours before administration of epidural meperidine. Cousins *et al.*⁷ reported that two of seven postoperative patients who received epidural meperidine 100 mg required naloxone for sedation approximately 30 minutes following injection, but respiratory depression was not discussed. Nor was it stated what anaesthetic technique was employed, or if the patients were given any parenteral narcotics or other CNS depressants.

Two controlled trials have not found any clinically significant respiratory depression. Rutter *et al.*¹³³ monitored respiratory rate and PaCO_2 following epidural meperidine 50 mg given to 20 postoperative patients. Respiratory rate decreased from a mean of 20 to a mean of 16–18, but the PaCO_2 did not change. Baraka *et al.*¹³⁴ gave epidural meperidine 100 mg with bupivacaine to 26 healthy primiparous women in labour. Respiratory rate, the only respiratory variable measured, decreased slightly in three patients, but no patient had a rate less than $16 \cdot \text{min}^{-1}$.

Albright¹³⁵ administered epidural meperidine 75 mg to patients after Caesarean section and monitored respiratory rate with a continuous apnoea monitor for 16 hours. One of

12 patients developed a sleeping respiratory rate of eight, five hours following drug administration. However, the respiratory rate when awake was 18, and the same patient had two subsequent doses without ill effects. No blood-gas analyses were done, and it was not stated whether the patient was cyanotic or unduly somnolent, or if she had received naloxone. Considering that there are no other reports of delayed respiratory depression following epidural meperidine and in view of its pharmacokinetic behaviour (*vide infra*), it is not proven that the patient in question had significant respiratory depression. This case again illustrates the problem of monitoring only respiratory rate.

Intrathecal meperidine has been employed as a spinal anaesthetic agent because of the drug's local anaesthetic properties.¹³⁶ The authors did not discuss the duration or nature of postoperative monitoring, but delayed respiratory depression was not mentioned. This is especially interesting because of the dose employed – 100 mg. One patient did become stuporous and required oxygen and assisted ventilation for 30 minutes. This occurred approximately 18 minutes after the intrathecal dose. This paper supports the impression that delayed respiratory depression is a rare event following a single-dose of epidural meperidine.

Sufentanil

Several case reports document the occurrence of severe respiratory depression following either single or repeated doses of epidural sufentanil. Blackburn¹³⁷ reported two patients who suffered respiratory arrests following four to seven doses of epidural sufentanil 50 μg over 20–22 hours. Vercauteren *et al.*¹³⁸ reported extreme bradypnoea and hypercapnia in two patients after thoracotomy following a first dose of 50 μg given postoperatively. These patients received intravenous morphine 0.3 $\text{mg} \cdot \text{kg}^{-1}$ intraoperatively.

Epidural sufentanil has been administered either as a single dose or as repeated boluses for postoperative analgesia. Following urologic surgery in children epidural sufentanil 0.75 $\mu\text{g} \cdot \text{kg}^{-1}$ was not associated with any apnoeic episodes or abnormally slow respiratory rates. However, monitoring was not continuous and apnoea was not defined. Although minute ventilation and PETCO_2 did not change significantly, the slope of the CO_2 response curve was decreased at 30 and 60 minutes following injection.¹³⁹

Madej and Strunin¹⁴⁰ compared epidural sufentanil with fentanyl for postoperative analgesia in patients undergoing Caesarean section with epidural anaesthesia. These investigators monitored PETCO_2 continuously for nine hours from the beginning of surgery. Patients received either fentanyl 100 μg or sufentanil 10, 20, 30, or 50 μg . Although 4 of 50 patients developed delayed bradyp-

noea of 8 breaths $\cdot$ min⁻¹ within 20 minutes of opiate administration (three received fentanyl and one received sufentanil 50 μ g), none of these four had a clinically significant elevation of PETCO₂. Two sufentanil patients developed a PETCO₂ of 46–47 mmHg 25 minutes following administration of 20 or 30 μ g. No episodes of apnoea were detected. However, apnoea was not defined and the validity of monitoring PETCO₂ is uncertain.

Whiting *et al.*¹⁴¹ administered sufentanil 30, 50, or 75 μ g via lumbar epidural catheters to patients after thoracotomy. Repeat doses were given as required, but at intervals of not less than 30 minutes. Patients were monitored continuously using respiratory inductance plethysmography for 24 hours postoperatively and arterial blood-gas analyses were performed at 30 and 60 minutes, then at four hourly intervals. In all groups the PaCO₂ was significantly elevated at 30 minutes and apnoeic episodes occurred in over 50 per cent of patients. In the group receiving 75 μ g, three of seven patients developed severe respiratory depression, including one who had a respiratory arrest requiring re-intubation after a single dose.

Van der Auwera *et al.*¹⁴² compared epidural sufentanil with epidural morphine in patients undergoing abdominal surgery. Respiratory rate and PaCO₂ were monitored intermittently for 12 hours or until parenteral analgesics were required following administration of sufentanil 50 μ g or morphine 5 mg. The authors found no clinically significant increase in mean PaCO₂ but 2 of 15 patients given sufentanil developed marked bradypnoea (respiratory rate of 4 $\cdot$ min⁻¹) within ten minutes of the dose. Others have found little evidence of significant respiratory depression. Donadoni *et al.*^{143,144} administered epidural sufentanil 15–75 μ g to ASA Status I orthopaedic patients and found no significant changes in respiratory rate or PaCO₂.

In summary, the data concerning epidural sufentanil are not consistent. The marked, life-threatening respiratory depression found by Whiting *et al.* was not found in children or post-partum patients, or in the healthy orthopaedic patients studied by Donadoni. In part this may reflect different study populations, with thoracotomy patients being at higher risk of postoperative respiratory insufficiency. Also, non-continuous monitoring techniques may underestimate the true incidence of clinically significant events. The limited information available suggests that late respiratory depression following a single dose of epidural sufentanil is unlikely.

Other opioids

Numerous other opioids have been administered via the epidural route for postoperative analgesia. Diacetylmorphine has been reported to cause both early and delayed respiratory depression when administered by both the

epidural and intrathecal routes.^{96,145–147} The incidence of clinically significant problems is unknown.

In volunteers, epidural alfentanil 15 μ g $\cdot$ kg⁻¹ did not alter resting PaCO₂ but did decrease the slope of the CO₂ response curve for at least 90 minutes following administration. The same dose of alfentanil given intramuscularly depressed the CO₂ response curve at 15 but not 45 or 90 minutes.¹⁴⁸ Limited clinical evidence suggests that 30 μ g $\cdot$ kg⁻¹, but not 15 μ g $\cdot$ kg⁻¹, may produce early, severe respiratory depression.¹⁴⁹

Buprenorphine, a lipophilic mu receptor partial agonist, is associated with early and persistent respiratory depression in both patients¹⁵⁰ and volunteers.¹⁵¹ Buprenorphine dissociates very slowly from mu receptors. As a result, naloxone, even in large doses, may be ineffective in reversing respiratory depression once it develops.¹⁵²

Abboud *et al.*¹¹⁸ measured CO₂ responsiveness in patients after Caesarean section who received either epidural morphine or butorphanol. The CO₂ response curve was depressed for at least 12–16 hours following 2–4 mg of butorphanol. Morphine had a greater depressant effect, but also provided more complete analgesia.

Methadone,¹⁵³ pentazocine,¹⁵⁴ hydromorphone,¹⁵⁵ and nalbuphine¹⁵⁶ have also been administered via the epidural route, but at present there is insufficient data to form any conclusions concerning respiratory depression associated with these drugs.

Mechanisms of respiratory depression

Introduction

To understand how spinal opioids may result in respiratory depression it is appropriate to review briefly the anatomy and physiology of respiratory control, and how opioids, by any route, may affect this control.

Control of ventilation

The neural control of ventilation is complex. The respiratory rhythm will be generated within the isolated medulla, but in the intact subject rate and rhythm are influenced by afferent signals from supra-spinal sources (e.g., voluntary breath-holding), the vagus nerves, and most importantly, peripheral and central chemoreceptors. The paired peripheral chemoreceptors, the carotid bodies, are stimulated by hypoxia, a decrease in arterial pH, and, to a lesser degree, by an elevation of PaCO₂. Afferent signals travel via the glossopharyngeal nerve to the respiratory neurones of the medulla.

The central chemoreceptors account for approximately 80 per cent of the response to carbon dioxide but are not responsive to (or are depressed by) hypoxia. These chemoreceptors lie very superficially, 0.2 mm, beneath the antero-lateral surface of the medulla and are thought to

have neuronal connections with the dorsal and ventral respiratory groups of neurons which are more deeply imbedded within the substance of the medulla. In the past it was thought that the neurons of the respiratory centre, i.e., the dorsal and ventral respiratory groups, were directly responsive to CO_2 . However, it is now felt that the more superficial chemoreceptors respond to changes in cerebrospinal fluid pH. This is consistent with the knowledge that CO_2 diffuses readily into the CSF and that respiration is stimulated if these areas are bathed with mock CSF having an elevated PCO_2 or lower pH. For a comprehensive discussion the reader is directed to Nunn¹⁵⁷ and Lambertsen.^{158,159}

Respiratory effects of opioids

Morphine and related opioids given in sufficient doses decrease minute ventilation by decreasing respiratory rate, tidal volume, or both. They decrease the response to hypoxia, and shift the CO_2 response curve down and to the right. In addition, breathing may become irregular and periodic.^{36,160}

Morphine and other agonist drugs have both direct and indirect effects on breathing. Morphine will cause respiratory depression when applied directly to the chemosensitive anterolateral surface of the medulla,^{161,162} following injection directly into the fourth or lateral ventricles^{163,164} or following iontophoretic injection into the pontine or medullary respiratory centres.¹⁶⁵ Hurle *et al.*¹⁶¹ state that respiratory depression is less following intraventricular administration than following subarachnoid administration adjacent to the ventral surface of the medulla. The significance of respiratory depression following iontophoretic injection of morphine into the respiratory nuclei is uncertain. The lungs of all animals were ventilated artificially to maintain normocapnia under halothane anesthesia and respiratory depression was inferred from decreases in bulbar neuronal and phrenic nerve electrical activity. How the animals would have responded to a CO_2 challenge is unknown. It must also be noted that the work cited above involves animal research, and the degree to which one can extrapolate the results to man is unknown.

Several subclasses of opioid receptors exist. Mu receptors mediate analgesia and respiratory depression in particular. Kappa receptors mediate analgesia and sedation and there is some evidence that kappa receptors may be present in large numbers in the human spinal cord.¹⁶⁶ Whether kappa agonist activity contributes to respiratory depression is uncertain.¹⁶⁰ Morphine and related drugs are mu and kappa agonists. Drugs with agonist/antagonist properties, such as nalbuphine and pentazocine, are mu-receptor antagonists and kappa and sigma agonists.¹⁶⁰

Analgesic doses of opioids may depress respiration

indirectly. Pain causes respiratory stimulation by generalized arousal,¹⁵⁸ a response attenuated by adequate analgesia. The release of substance P, a neurotransmitter released in response to nociceptive stimuli, is inhibited by opioids. Substance P has been shown to stimulate respiration following injection into the cerebral ventricles or brainstem subarachnoid space.¹⁶³ Its relevance to narcotic-induced respiratory depression has not been established.

Pharmacokinetics

There is general agreement that spinal opioids result in respiratory depression primarily by direct depression of the respiratory nuclei and/or the chemosensitive areas of the brain stem.^{14,163,164} The pharmacokinetics are complex.

Following epidural administration drugs may leave the epidural space by vascular absorption or may penetrate the dura and enter the subarachnoid space. Once in the CSF drugs may enter the spinal cord, be absorbed into the vasculature, spread cephalad within the CSF, or possibly undergo metabolism. Respiratory depressant concentrations of opioids within the brain stem may occur if either blood concentrations or brain-stem CSF concentrations are sufficiently high. Elimination from the central nervous system results from direct vascular uptake from neural tissues or from diffusion back into the CSF and subsequent elimination at the subarachnoid granulations.¹⁶

VASCULAR UPTAKE

There is evidence that systemic uptake of opioids from the epidural space is similar to or faster than that following intramuscular injection.^{8,14,141,164,167} However, serum concentrations decline more rapidly following epidural administration. When morphine,¹⁶⁷⁻¹⁷⁰ meperidine,^{167,171} or fentanyl^{126,172,173} are administered in their usual doses, post-injection serum concentrations after the first hour are less than those associated with adequate postoperative analgesia or respiratory depression. Negre *et al.*¹²⁶ found decreased CO_2 responsiveness following epidural but not intramuscular fentanyl for two hours after injection, and in two of nine subjects in the epidural group these changes persisted for three hours. At all times during this study the serum concentrations in the epidural group were significantly lower than in the intramuscular group. This implies that although systemic uptake of epidural opioids may be important, it does not account for all instances of early respiratory depression.

DURAL PENETRATION

Dural penetration of epidurally administered opioids into the CSF is related to the physicochemical properties of

the drugs. Molecular weight has been suggested as the major determinant of dural transfer¹⁸¹ but lipophilicity is felt to be of primary importance by most investigators.^{14,164,167,175} For morphine, which is relatively hydrophilic, peak CSF levels occur at one to two hours post-injection.^{8,167} For meperidine, a highly lipophilic drug, this peak occurs at 15–45 minutes. For other highly lipophilic drugs such as fentanyl or sufentanil, rapid dural penetration has been inferred from the rapid onset of analgesia when compared with morphine. Although the rate of dural penetration is greater with highly lipophilic opioids, the amount of drug which enters the CSF may be similar. Sjostrom *et al.*¹⁶⁷ found that approximately 3.6–3.7 per cent of either epidural morphine or meperidine entered the subarachnoid space. Whether bioavailability is similar for other lipophilic opioids is not known.

CEPHALAD FLOW IN CSF

Lipophilicity of epidurally administered opioids is also a major determinant of cephalad spread within the CSF and resultant respiratory depression. With the exception of morphine, epidurally administered opioids are highly lipophilic (Table IV), and will therefore diffuse readily into neural tissues, across the dura if the concentration gradient is favourable, or into the circulation. As a result the CSF concentrations of these highly lipophilic drugs tend to decrease rapidly, with corresponding reductions in cephalad spread. For morphine and meperidine these pharmacokinetic differences have been quantified. Sjostrom *et al.*¹⁶⁷ calculated CSF pharmacokinetic data for epidurally administered morphine and meperidine. In the subarachnoid space, which includes both the CSF and the neural tissue, the elimination half-lives for morphine and meperidine were not statistically different. However, from 2 to 15 hours post-dose, the normalized CSF concentration (i.e., correcting for differences in doses) of morphine was up to four times greater than the meperidine concentration. In addition, Sjostrom *et al.*¹⁶⁷ assert that beyond eight hours, only ten per cent of the remaining subarachnoid meperidine remained within the CSF, whereas for morphine the corresponding value was 45 per cent. Although similar pharmacokinetic data does not exist for the very lipophilic opioids (Table IV), it is probable that they behave in a manner similar to meperidine rather than morphine. It is this lipophobic property of morphine, setting it apart from other epidurally administered opioids, which accounts for its late cephalad spread and delayed respiratory depression.

The rate and degree of cephalad spread of intrathecal opioids in man has not been adequately studied, in large part due to the obvious technical and ethical constraints associated with repeated cisternal CSF sampling. In an anaesthetized, spontaneously breathing baboon cisternal

TABLE IV Octanol:water partition coefficients at pH 7.4. Adapted from Cousins and Mather¹⁴ and Hug¹⁷⁰

Opioid	Lipid solubility
Morphine	1.42
Meperidine	38.8
Methadone	116
Alfentanil	126
Fentanyl	813
Sufentanil	1778

CSF concentrations of morphine peaked at approximately three hours following lumbar intrathecal morphine.¹⁷⁶ However, the concentrations found were much lower than those predicted for the lumbar subarachnoid space on the basis of other published reports. These same investigators found that brain-stem uptake of tritiated morphine was higher (by a factor of 100) six hours after injection than at 1 and 24 hours.¹⁷⁷

Bromage *et al.*¹⁷⁸ provided indirect evidence for the cephalad spread of epidural morphine. Following administration of epidural morphine 10 mg to young, healthy volunteers, dermatomal levels of sensitivity to ice and pin scratch were determined at regular intervals. By six hours, eight of ten subjects had trigeminal analgesia which implied cephalad spread to the level of the brain stem.

For more lipophilic drugs, the evidence for cephalad spread is conflicting. In chronically instrumented sheep given morphine, sucrose, and methadone simultaneously via a lumbar epidural catheter, cisternal CSF concentrations of morphine and sucrose peaked at approximately three hours. In contrast, no methadone was detectable up to five hours following administration.¹⁷⁹

Gourlay *et al.*^{180,181} have studied cephalad spread of epidural morphine and meperidine in humans. They administered morphine and meperidine simultaneously via a lumbar epidural catheter to patients with metastatic cancer. CSF was sampled once in each patient from the C₇-T₁ interspace. Sampling was done at 10, 30, and 60 minutes, then hourly up to six hours. The authors found that morphine concentrations peaked at two to three hours, consistent with the results of other investigators. However, meperidine peaked much earlier, and at a greater concentration than morphine. Two hours following injection meperidine concentrations were lower than morphine levels. Gourlay *et al.* also cite unpublished work in which fentanyl, a highly lipophilic compound, did not spread to the C₇-T₁ interspace following lumbar epidural administration. It should be emphasized that sampling was done at C₇-T₁, and the degree to which meperidine reaches the cisterna magna is unknown.

The reader should appreciate that the most important factor limiting the occurrence of clinically significant respiratory depression following epidural or subarachnoid opioids is the non-homogeneous spread of these drugs throughout the subarachnoid space (including the intracranial subarachnoid space and neural tissues), with the resulting concentration gradients between lumbar and intracranial CSF and between intracranial CSF and the neural tissues of the brain stem. To illustrate this point, Cousins and Mather¹⁴ noted that the CNS uptake of intravenous morphine was on the order of 0.1 per cent. Therefore, following intravenous morphine 100 mg, an apnoeic dose, only 100 µg would penetrate into the CNS. This compares with 250–500 µg of morphine typically administered intrathecally.

To summarize the foregoing discussion, it is widely agreed that epidural morphine spreads in a cephalad direction to reach the cisterna magna within six hours. For more lipophilic narcotics the evidence is contradictory. Gourlay *et al.*^{180,181} presented evidence to support the rapid cephalad flow of epidurally administered meperidine. For fentanyl¹⁸⁰ and methadone¹⁷⁹ no such cephalad spread was detected. Finally, Negre *et al.*¹²⁷ demonstrated depression of the CO₂ response curve two to three hours following epidural fentanyl when the serum concentrations of the drug were too low to be responsible for the effect. This is difficult to reconcile with the results of Gourlay *et al.*^{180,181} Although the degree of cephalad spread of lipophilic opioids is not yet known, both pharmacokinetic and clinical evidence supports the position that, when given as a single dose, they do not cause delayed respiratory depression. It must be noted that the work cited above involved either animal models or non-surgical volunteers. Coughing, vomiting, or artificial ventilation, all common in the perioperative and postoperative periods, may increase the circulation of the spinal cord CSF. This may result in more rapid and greater cephalad spread, and probably contributes to the unpredictable nature of both early and delayed respiratory depression.¹⁴

Incidence of respiratory depression and patients at risk

Early, measurable respiratory depression is frequently detectable for both morphine and the more lipophilic opioids following a single epidural dose. With repeated boluses or continuous infusions the limited evidence suggests that this respiratory depression persists, at least for the first 24 hours. Late respiratory depression may be detectable up to 24 hours following a single dose of epidural morphine, but not following a single dose of a lipophilic opioid.

The true incidence of clinically significant respiratory

TABLE V Factors predisposing to the development of respiratory depression following epidural opioids. Ref: Cousins and Mather,¹⁴ Rawal *et al.*,¹⁰¹ Stenseth *et al.*³¹

<i>Drug factors</i>
Hydrophilic drug (i.e., morphine)
Large doses
Repeated doses
Concomitant administration of parenteral opioids or other CNS depressants.
<i>Patient factors</i>
Elderly or debilitated
Co-existing respiratory disease
Thoracic epidural
High sensitivity to opioids (i.e., no previous exposure to opioids)
Intrathecal administration
Raised intrathoracic pressure (e.g., controlled ventilation, coughing, vomiting)

depression is not known. The overall incidence has been stated as 0.09–3 per cent,^{101,116} and this value may be much lower if one excludes patients also given parenteral narcotics. In any event, a single figure for the incidence of respiratory depression may be misleading. Clearly, some patients will be at greater risk; some of the relevant risk factors are summarized in Table V. *Even in the absence of any identifiable risk factors, some patients will develop life-threatening respiratory depression.*

In obstetrics, epidural morphine may be administered following epidural anaesthesia for Caesarean section. In this situation the risk of clinically significant respiratory depression appears to be very low. This is attributable to the youth and general good health of this patient population. In addition, the increased respiratory drive associated with pregnancy may persist into the immediate post-partum period. Whether this is protective is not known. The reader is reminded, however, that although the risk is low, it is not zero. If a patient receives an inadvertent dose of subarachnoid morphine due to catheter migration, for example, severe, delayed respiratory depression should be expected.

Clinical implications and areas for future investigation

The safe use of spinal opioids requires knowledgeable medical and nursing staff, appropriate monitoring, and clear instructions for management of supplemental analgesia, monitoring, and treatment of complications. High-risk patients must be managed in an intensive care or step-down unit, where respiratory rate, somnolence, and often arterial blood gases can be monitored. Transient hypoventilation or apnoea may occur, and continuous respiratory monitoring or pulse oximetry is highly recommended. For patients who have undergone major surgery

supplemental oxygen should be continued for at least 24 hours.

It is the opinion of the authors that, with the possible exception of post-Caesarean section patients, no patient given a single dose of epidural or intrathecal morphine should be transferred to a general surgical floor within 18–24 hours of receiving the drug. For the patient who has received multiple doses over a protracted period without complications, this interval may be reduced. For patients given single, repeated, or infusion doses of highly lipophilic opioids, the available evidence supports the resumption of routine monitoring and care four to six hours following the last dose or cessation of the infusion. Others dispute this opinion. Ready *et al.*¹¹⁷ assert that postoperative patients receiving epidural or subarachnoid opiates can be managed appropriately on the general wards if electronic respiratory monitoring is available for high-risk patients. High-risk patients include older, sicker patients having lengthy, high abdominal or thoracic procedures, patients given more than 6 mg of epidural morphine or 0.5 mg of intrathecal morphine, and patients who receive significant doses of parenteral narcotics during the perioperative period.

The use of epidural morphine in after Caesarean section may be a special case. Monitoring of respiratory rate and somnolence in these patients on the regular post-partum ward is acceptable if the criteria mentioned above are met. Of these criteria, the most important is education of the nursing staff. An example of postoperative orders is given in Table VI. As the availability of pulse oximeters increases, continuous pulse oximetry may further increase the margin of safety in this patient population.

Several techniques exist which may decrease the incidence and severity of respiratory depression. These include continuous infusions of highly lipophilic drugs, epidural administration of mixed agonist/antagonist drugs such as nalbuphine,¹⁸² and prophylactic low-dose intravenous naloxone infusion.¹⁸³ Whatever techniques are chosen, investigators must determine the degree to which respiratory depression is clinically significant. This implies that clinical studies should employ monitoring techniques which will detect not only trends reflected by a gradual change in respiratory rate or PaCO₂, but also continuous monitoring techniques capable of detecting transient events such as episodes of apnoea, severe hypoventilation, or hypoxaemia.

Finally, two fundamental questions have yet to be answered. When administered in equianalgesic doses, do spinal opioids produce respiratory depression more severe than that seen with parenteral administration? And does the improved analgesia attributed to spinal opioids alter postoperative morbidity and mortality? The limited data available suggest that episodes of bradypnoea and apnoea

TABLE VI Example orders following epidural morphine

Epidural morphine — mg given at — hours.
Monitor respiratory rate q 30 min for 2 hours, then hourly for 22 hours.
If respiratory rate <10, or if patient excessively somnolent, rouse patient, encourage deep breathing, give oxygen, and call anaesthetist.
If respiratory rate <8, rouse patient, encourage deep breathing, give oxygen and give naloxone 0.2–0.4 mg IV stat. Call anaesthetist stat.
No other narcotics are to be given without specific orders from anaesthetist.
For pruritis give diphenhydramine 25–50 mg IV/IM q 4–6 h.
For nausea give dimenhydrinate 25–50 mg IV/IM q 4–6 h.
Call anaesthetist if analgesia is inadequate or for any other problems.

are more frequent when analgesia is provided with epidural rather than intravenous morphine, at least in post-thoracotomy patients.¹¹⁵ With respect to morbidity and mortality, Shulman *et al.*¹⁸⁴ demonstrated better lung function in patients after thoracotomy given epidural versus intravenous morphine, but pain scores were lower in the epidural group. There is also some evidence that high-risk surgical patients have less morbidity and lower mortality when managed with epidural opioid analgesia.¹⁸⁵ At present, however, these data are inconclusive, and the questions remain unresolved.

Summary

The administration of epidural and intrathecal opioids for the control of postoperative pain often provides superb analgesia of long duration with minimal effects on the central nervous system. However, side effects do occur, and the most dangerous is respiratory depression, either early or delayed.

The true incidence and clinical significance of respiratory depression following spinal opioids remain poorly defined. This is attributable to a paucity of well designed, prospective studies; these studies should monitor patients continuously and non-invasively during the postoperative period and during sleep. For drugs such as morphine, a highly hydrophobic, long-acting drug, such monitoring may be required for at least 24 hours following a single dose.

For morphine, early, clinically significant respiratory depression is uncommon if the patient does not receive parenteral opioids concomitantly. However, late respiratory depression may persist for 24 hours following a single dose. This respiratory depression may manifest itself as transient apnoeas or periods of severe hypoventilation during sleep, rather than as a low respiratory rate with hypercapnia. For more lipophilic opioids, respiratory depression typically occurs soon after administration of a single dose.

Opioids depress respiration when they are present, in sufficient concentration, in the chemosensitive areas and respiratory nuclei of the brain stem. Early respiratory depression is associated with systemic uptake into the circulation and subsequent delivery to the CNS. Late respiratory depression, seen with morphine, is attributed to cephalad spread of the drug within the CSF.

Clearly, some patients are at greater risk of developing clinically significant respiratory depression following spinal opioid administration. These include older, sicker patients, patients with pre-existing respiratory problems, and patients who receive parenteral opioids peri- or postoperatively. However, some patients with no identifiable risk factors will develop life-threatening respiratory depression.

To employ these potent analgesic techniques safely, patients must be monitored adequately by knowledgeable medical and nursing staff. It is not adequate simply to measure respiratory rate on an hourly basis. As a minimum, both respiratory rate and somnolence should be monitored. Patients at greater risk should be monitored in an intensive care or step-down unit. Apnoea monitors are useful for the detection of central apnoeas, but may fail to detect obstructive apnoeas. Continuous pulse oximetry may provide an added measure of safety for these patients.

Finally, anaesthetists must ask themselves whether spinal opioids are worth the effort. Despite much research in the area, there is still inadequate evidence to decide whether equianalgesic doses of spinal and parenteral opioids differ in the degree of respiratory depression they cause. If we can provide improved analgesia by this route safely, does it affect outcome; are morbidity and mortality lessened? Until these issues are resolved, the value of spinal opioids in the management of postoperative pain is unproven.

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Résumé

L'injection d'opiacés par voie péridurale ou intra-rachidienne pour fin d'analgésie post-opératoire est efficace mais amène chez certains une dépression respiratoire importante. Cet article aborde les moyens de détection et de mesure de la dépression respiratoire associée à ces modes d'administration et fait une revue de la littérature pertinente. Nous revoyons aussi le profil pharmacocinétique des opiacés rachidiens en relation avec leur pouvoir de dépression respiratoire. Finalement, nous en discutons les implications cliniques de même que les champs de recherche s'offrant à nous.