The prime function of anaesthetists is to relieve pain. The technical skills and pharmacological knowledge required to do this during surgery place them in an ideal position to treat pain in other situations. Thus anaesthetists have been at the forefront of developments in the relief of pain during labour and devote much attention to the relief of chronic pain of whatever aetiology. Indeed, active societies exist in both these disciplines and have been vigorous in the promotion of research and teaching, even though such activities are expensive in terms of time and manpower.

Postoperative pain relief, however, has been sadly ignored [189] and members of the public [114], and even eminent members of the profession [67,162], have been moved to comment on the severity of pain after surgery and the lack of efforts to relieve it. The standard method of prescribing a fixed dose of opioid to be given at limited time intervals, and with administration being delegated to a nurse, is manifestly a totally inadequate method of producing postoperative analgesia. Extradural block with local anaesthetic agents will abolish postoperative pain, but its use has been limited by anxiety about hypotension, tachyphylaxis, systemic toxicity, the technical difficulty of insertion of a catheter into the thoracic extradural space and the problems of postoperative surveillance. Other nerve blocks, particularly intercostal [125], can also be very successful, but their use is restricted by the feasibility of repeating them in the postoperative period.

Patient controlled analgesia was introduced in an attempt to overcome many of these problems and has proved to be a successful method after surgery [39,182]. It can also be used as a method by which the efficacy of other analgesic techniques may be assessed by registering the number of demands for additional analgesia [115]. However, it does require the use of sophisticated and relatively expensive apparatus and the maximum dose of drug and minimum time interval between doses are set by the doctor, who must err on the side of safety in these choices. Experience of such apparatus has indicated that the patients chose a balance between analgesia and the incidence and severity of side effects.

The discovery of opioid receptors in the central nervous system, in particular their existence in the spinal cord, came at an opportune time and raised exciting new possibilities in the management of severe pain.

**HISTORICAL BACKGROUND**

The steps leading to the eventual use of spinal opioids in man are shown in Table 1. In 1976, Yaksh and Rudy [206] showed, in rats, that opioids applied directly to the spinal cord and remaining localized, produced intense analgesia. It was suggested [204] that the receptors through which the drugs were acting were situated presynaptically on afferent terminals in the substantia gelatinosa and that the effect was to block the release of the neurotransmitter associated with nociceptive transmission [96]. In this region,

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Demonstration of existence of opioid receptors [82]</td>
</tr>
<tr>
<td>1973</td>
<td>Demonstration of opioid receptors in the brain [148]</td>
</tr>
<tr>
<td>1976</td>
<td>Demonstration in animals of analgesia produced by spinally applied opioids [206]</td>
</tr>
<tr>
<td>1979</td>
<td>Intrathecal opioids first used in man [193]</td>
</tr>
</tbody>
</table>

Extradural opioids first used in man [18]
TABLE II. Predicted advantages of spinally applied opioids

- Segmental analgesia with no sensory or motor loss.
- No autonomic block with consequent absence of hypotension.
- No central or respiratory depression.
- Availability of a large number of drugs.
- Existence of a specific antagonist.

opioids have been shown in vivo to antagonize the release of one putative transmitter, substance P [205]. In 1979, morphine was used intrathecally [193] and extradurally [18] in man, and in small doses produced prolonged analgesia in patients with chronic pain.

A number of advantages were predicted for this new method of analgesia (table II). It was hoped that segmental analgesia would be produced by only small doses of drug, without loss of any other sensory modality or interference with motor function. There should be no autonomic block and hence no hypotension, which is the main factor limiting the use of extradural local anaesthetics; there should also be no interference with bladder function. Inadvertent intravascular injection would be unlikely to have the serious consequences associated with i.v. local anaesthetics. Above all, was the possibility of divorcing respiratory depression from analgesia with opioid drugs. A range of opioids was available, the different durations of action of which would match different clinical situations. Finally, a specific antagonist was already available in the form of naloxone, thus guaranteeing prompt antagonism of any unwanted sequelae.

After the first reports, there was a surge of publications attesting to the efficacy of this new technique. Winnie [200] commented that never before had sophisticated laboratory research moved so rapidly into the clinical field. Unfortunately, many of these initial reports ignored the fundamental principles of properly conducted clinical trials, and claimed complete analgesia of very prolonged duration with no complications. One of the main reasons for this was the lack of any “central” control for the studies that were being performed, because there was no requirement for such control: neither the drugs nor the techniques were new; it was the application that was new [200].

The purpose of this review is to produce some logical conclusions on the use of spinal opioids and consideration will be confined to their use in acute pain. In order to do this it is necessary to:

1. verify the points documented in table II
2. make some comparison of the available drugs
3. assess the merits of the extradural compared with the intrathecal route of administration
4. compare extradural and intrathecal opioids with other methods of analgesia
5. assess the nature, incidence and severity of complications.

ANALGESIC EFFECTS

Extradural Opioids

There is no doubt that opioids injected into the extradural space produce effective and often prolonged analgesia. Pethidine 100 mg in normal saline 10 ml was first used for postoperative pain in seven patients [55]. Onset of analgesia was rapid and complete between 12 and 20 min after injection. At this time, blood concentrations of pethidine were less than those necessary to produce analgesia, and concentrations in cerebrospinal fluid (CSF) were high. Pain relief lasted an average of 6 h and there was no evidence of sensory, motor or autonomic block.

Morphine, in doses varying from 2 mg [161] to 0.1 mg kg⁻¹ [195], has been the most widely used drug. Analgesia tends to be slow in onset, taking up to 60 min [59, 121, 195] to develop, but can last for more than 24 h, with many reports mentioning that only one injection was required after operation. No evidence of block of any other sensation or of motor power has been revealed by these studies and hypotension has not been a problem.

Available evidence confirms that analgesia results from a regional rather than a systemic effect, although there may be some initial contribution from the latter. Pharmacokinetic studies have found no relationship between quality of analgesia and plasma concentrations of the drug, which have been well below reported “analgesic” concentrations [134, 178, 195, 208]. Indeed, excellent analgesia may be present with no morphine detectable in the plasma. Experimental work in volunteers also confirms the segmental effect of extradural morphine. Torda and colleagues [188] found that morphine 3 or 4 mg injected into the lumbar extradural space resulted in an increase in pain threshold in the legs, but not on the forehead, while i.m. morphine raised the threshold in both areas. Similarly, extradural morphine 3.5 or 7.5 mg markedly delayed the onset of experimentally induced ischaemic pain in the lower.
limbs, but not in the arms. This effect was still present 6 h after injection [185]. Subcutaneous morphine had no significant effect on the times to pain perception in either limb and the authors concluded that the extradural morphine produced analgesia by a regional effect rather than by systemic absorption.

A greater improvement in postoperative pulmonary function has been found by workers who compared extradural opioids with other analgesic techniques. Bromage, Camporesi and Chestnut [27] found that extradural opioids were more effective than i.v. morphine in restoring FEV₁ towards preoperative values. Rybro and colleagues [168] found that 67% of patients who received i.m. morphine after upper abdominal surgery had radiological changes on chest x-ray on the 2nd day after operation, compared with 21%, who had received 4-mg doses of morphine extradurally. After cholecystectomy, analgesia with extradural morphine resulted in a smaller decrease in peak expiratory flow than was associated with either i.m. opioids or intercostal block with bupivacaine [157]. Bonnet and colleagues [24] found lower pain scores with extradural morphine than with i.m. injections of the analgesic baralgin, but no difference in VC, FEV₁, or FRC. A decrease in postoperative morbidity [177] and possibly mortality [207] has also been reported. However, Hjortso and colleagues [89], using a mixture of extradural morphine and bupivacaine, found that although pain scores were lower than with i.m. morphine after abdominal surgery, there was no difference between the groups in terms of postoperative mortality, pneumonia, arrhythmias, wound complications, deep vein thrombosis or convalescence.

**Dose of morphine**

Despite the widespread use of extradural morphine there have been few dose finding studies. Morphine 2 mg is effective in relieving pain after lower limb orthopaedic surgery [121, 161], but ineffective after upper and lower abdominal surgery [57, 167]. However, 5 mg and 10 mg produced prolonged analgesia after lower abdominal operations, although no additional benefit resulted from the larger dose [57]. In particular, very prolonged analgesia has been noted to follow morphine 5 mg after Caesarean section [202]. Martin and colleagues [121] compared five doses of morphine (0.5–8.0 mg) after orthopaedic surgery and found that doses of 2.0 mg and greater were equally effective. Similar results were found by Lanz, Kehrberger and Theiss [106], who found that patients who received 2.0 mg or more were less likely to require additional analgesia. However, they also found that the incidence of urinary retention and pruritis increased dose dependently, and recommended 3.0 mg as being the best compromise between analgesia and an acceptable incidence of side effects. A dose of 4 mg produced excellent analgesia following hip arthroplasty and major lower limb surgery, but 6 mg was required in the thoracic extradural space after laparotomy or thoracotomy [181].

The majority of workers have used a fixed dose of morphine to produce analgesia after operation. In view of the known very wide variation in the individual response to opioids, it would seem much more rational to titrate the dose until the desired effect is reached. This approach was used by Bromage, Camporesi and Chestnut [27] when comparing three opioids (morphine, hydromorphone and methadone), extradural local anaesthetics and i.v. morphine for pain relief after upper abdominal surgery. They found that the dose of extradural morphine required to produce effective analgesia was very similar to that used i.v., but that the former route produced much more prolonged analgesia with significantly less central depression. Recently, patient controlled analgesia has been used by the extradural route [178]. Morphine in increments of 1 mg, with a minimum interval of 30 min between doses, or pethidine 20 mg, both produced satisfactory analgesia, there being no difference between the drugs. The authors did comment that large interindividual variations made it impossible to recommend a standard dose of either drug for analgesia of predictable duration and with a minimum of adverse effects.

**Other drugs**

Most narcotic analgesics have been used extradurally in the management of postoperative pain, by either bolus injection or continuous infusion (table III) and effective analgesia has been reported after the use of them all. Fentanyl has been given using a patient controlled system, when no difference was found in fentanyl usage between the extradural and i.v. routes [74]. Meptazinol 90 mg was found by Verborgh, Van Der Awera and Camu [191] to produce effective analgesia, but others found smaller doses to be ineffective and did not recommend its use [22,
Table III. Opioids used extradurally

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>25–100 mg</td>
<td>[31, 55, 70, 81, 167]</td>
</tr>
<tr>
<td></td>
<td>0.75 mg kg⁻¹</td>
<td>[145]</td>
</tr>
<tr>
<td></td>
<td>1.0 mg kg⁻¹</td>
<td>[164]</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>0.5–1.0 mg</td>
<td>[14, 16, 116, 120, 137]</td>
</tr>
<tr>
<td></td>
<td>0.1 mg kg⁻¹</td>
<td>[94]</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 µg</td>
<td>[167]</td>
</tr>
<tr>
<td></td>
<td>200 µg</td>
<td>[112]</td>
</tr>
<tr>
<td></td>
<td>20–80 µg h⁻¹</td>
<td>[19, 47, 198]</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>200 µg h⁻¹</td>
<td>[47, 48]</td>
</tr>
<tr>
<td></td>
<td>15–30 µg</td>
<td>[42]</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>15–75 µg</td>
<td>[51, 65, 66, 117]</td>
</tr>
<tr>
<td></td>
<td>3 µg kg⁻¹ h⁻¹</td>
<td>[43]</td>
</tr>
<tr>
<td>Lofentanil</td>
<td>5 µg</td>
<td>[21]</td>
</tr>
<tr>
<td>Methadone</td>
<td>4–6 mg</td>
<td>[17, 197]</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>60–300 µg</td>
<td>[21, 107, 128, 129, 201]</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1 mg</td>
<td>[45]</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>30–90 mg</td>
<td>[22, 76, 191]</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>1–4 mg</td>
<td>[2, 101, 183]</td>
</tr>
<tr>
<td>Phenoperidine</td>
<td>2 mg</td>
<td>[116]</td>
</tr>
</tbody>
</table>

76]. Lofentanil produces very prolonged analgesia, but because of its extreme potency and very strong receptor binding characteristics, concern has been expressed that antagonism might be difficult [21].

It would seem more sensible to use the shorter acting drugs like fentanyl by continuous infusion, particularly after upper abdominal surgery, where it produces effective, but short lasting analgesia when given by bolus injection [167]. Welchew and Thornton [198] found that an extradural infusion of fentanyl at a rate of 60 µg h⁻¹ provided pain relief superior to that obtained with i.m. papaveretum. An infusion rate between 80 and 130 µg h⁻¹ was necessary to maintain adequate analgesia after abdominal aortic aneurysm surgery [19]. These authors commented that the short duration of action of fentanyl actually aided bed management in the intensive care unit, since it was not necessary to keep patients in the unit for so long after the last injection. Alfentanil would probably be an even better choice, and has been shown to produce excellent analgesia after major abdominal surgery, although experience with its use is limited [47, 48]. Despite its long duration of action, continuous infusions of morphine have been used to manage postoperative pain in doses varying from 100 to 400 µg h⁻¹ [58, 72, 73, 111].

Comparisons between the different opioids have been few, but it is unlikely that there will be any differences in analgesic efficacy between the drugs, but only in rate of onset, duration of action and incidence and severity of side effects. A major problem in comparing agents will be in choosing equipotent doses, because equivalent doses for systemic administration may well not apply to the extradural route. This has been shown to be the case for morphine and pethidine [178]. Thus Torda and Pybus [187] compared extradurally administered morphine 6 mg, methadone 6 mg, pethidine 60 mg and fentanyl 60 µg—doses which are regarded as being equipotent when given parenterally. There was no difference in the quality of analgesia, but the respective durations were 12.3 (SD 7.69) h, 8.7 (SD 5.89) h, 6.6 (SD 3.32) h and 5.7 (SD 3.72) h. No difference in the quality of analgesia was found between morphine and diamorphine [194].

Timing of injection

The efficacy of extradural morphine might be increased if it is given before the onset of pain [106]. The time to the first administration of an analgesic after surgery was almost twice as long in patients who had received extradural bupivacaine containing morphine 10 mg for the operative procedure than when bupivacaine was used alone [41]. In contrast, extradural morphine given for
the first time on the day after surgery failed to produce useful analgesia. It has also been noted that morphine 5 mg given after chloroprocaine with adrenaline had been used for Caesarean section had a slower onset and provided poorer analgesia than when plain chloroprocaine was used [150]. This resulted from the greater acidity of the local anaesthetic combined with adrenaline, resulting in a greater degree of ionization of the morphine. Others have found that morphine [86, 166] and diamorphine [137] given extradurally before surgery reduced opioid requirement in the immediate postoperative period.

**Effect on the stress response**

Neither morphine [166] nor diamorphine [137] administered extradurally influences the metabolic and hormonal responses to surgery, although cortisol concentrations were lower than controls in the postoperative period, probably reflecting the better pain relief. Extradural local anaesthetics suppress the increase in catecholamine concentrations noted in the immediate postoperative period, whereas extradural morphine can only suppress this response later on, indicating that pain might be a factor in the production of the stress response [166].

**Site of extradural injection**

It was originally stressed that the segmental nature of the analgesia produced by extradural opioids demanded the use of thoracic injection after thoracic and upper abdominal surgery. The thoracic approach is more difficult anatomically than the lumbar and potentially more dangerous [135], but there are numerous reports of the lumbar route providing satisfactory analgesia after upper abdominal and thoracic surgery [84, 134, 136, 197]. However, Sandler, Chovaz and Whiting [171] commented on the long latency between the injection of lumbar morphine and pain relief in the thoracic dermatomes. This may lead to additional doses of drug being given before they are necessary, so that complications are more likely to occur. Caudally administered morphine has provided satisfactory analgesia after perineal [25, 151] and even cardiac surgery [165].

The explanation may lie in the properties of morphine. It enters the CSF but, being of low lipid solubility, does not rapidly enter the spinal cord; it may thus spread widely and produce diffuse analgesia. After thoracic extradural morphine, the drug quickly appears in the CSF at lumbar level [132]. In contrast, a lipid soluble drug would rapidly enter the CSF and be more rapidly absorbed into the spinal cord and would be expected to produce a more sharply segmental analgesia. Controlled studies have not been performed to verify this hypothesis, and few have compared the effects of thoracic v. lumbar extradural morphine for upper abdominal surgery. Asari and colleagues [10] found that the analgesia produced by thoracic morphine was significantly superior to that given in the lumbar region. In contrast, a retrospective study [78] found no difference between the two routes in the number of patients requesting additional analgesia, but there was a considerable discrepancy in the numbers (92 thoracic v. 30 lumbar) and such studies cannot give any indication of the quality of analgesia. Similarly, Larsen and colleagues [109] reported no difference between thoracic and lumbar morphine 5 mg after upper abdominal surgery, but the first assessments were not made until 6 h after injection.

**Intrathecal Opioids**

Intrathecal opioids also produce satisfactory and prolonged relief of postoperative pain [131]. Originally, doses of morphine as large as 15–20 mg were used [170], but although analgesia is significantly longer with these large doses, the incidence of side effects is also significantly higher [169].

Most workers inject morphine intrathecally before the surgical procedure and have found similar results. When 0.8 mg was given intrathecally before cholecystectomy, less papaveretum was required in the first 24 h after operation than in a control group [69]. O'Neill and colleagues [139] found that intrathecal morphine 1 mg resulted in a significant decrease in the need for postoperative analgesia after spinal surgery. Intrathecal morphine 0.8 mg provided analgesia during aortic aneurysm surgery that was indistinguishable from moderate doses of parenteral opioids and was no more effective in attenuating the autonomic responses during the procedure [61]. The principal advantage was the avoidance of irregular and inadequate analgesia in the early and the most painful part of the postoperative period. Isaacson and colleagues [92] found that patients given morphine 0.5–1.0 mg intrathecally before abdominal aortic surgery could be extubated earlier in the postoperative
period and had significantly shorter stays in the intensive care unit and in hospital. Others have confirmed that earlier extubation is possible after major abdominal surgery when intrathecal morphine has been used, and also that its use is consistent with a stable perioperative haemodynamic state [44]. After coronary artery bypass surgery, patients who had received morphine 0.5 mg intrathecally required significantly less sodium nitroprusside and fewer i.v. supplements of morphine; there was, however, no difference in pain score [190].

The dose of morphine used by this route has been decreasing gradually. Recently, doses of 0.1 mg and 0.25 mg have been shown to produce excellent and prolonged analgesia (18.6 and 27.7 h, respectively) after Caesarean section [1]. However, there is a lack of information on the optimum dose of intrathecal morphine. A comparison of 0.3, 1.0 and 2.5 mg found that the low dose was associated with an inconsistent duration of analgesia and irritating side effects [93]. The larger doses provided excellent analgesia, but also a high incidence of respiratory depression.

Diamorphine [16, 144] and buprenorphine [37] have also been used intrathecally with good effect. Pethidine is the only drug that has been used successfully intrathecally as the sole anaesthetic agent, for genito-urinary [130] and lower abdominal and lower limb surgery [172]. The doses were 0.1 mg kg\(^{-1}\) and 100 mg, respectively; the effects may have been related to the local anaesthetic properties of pethidine.

Specialist Applications

**Obstetric analgesia**

Although extradural local anaesthetics will abolish the pain of labour, their use is associated with a number of problems. They are relatively short acting and so require repeated injection or a continuous infusion; hypotension is an ever present risk and accidental i.v. or intrathecal injection can have major consequences. The possibility of producing prolonged analgesia with small doses of opioids was therefore exciting.

However, extradural morphine has proved to be disappointing. Husemeyer and colleagues [91] found 2 mg to be totally ineffective in relieving the pain of the first stage of labour. Others found that 2.0 and 5.0 mg did not produce satisfactory pain relief, whereas 7.5 mg did during the first, but not the second stage of labour [90]; this is approaching the systemic dose. Extradural fentanyl 150–200 \(\mu\)g produced excellent pain relief until the late first stage, but was inadequate during the latter part of the first stage and during the second, when pain was at its worst [38]. Addition of fentanyl 80 \(\mu\)g to the test dose of bupivacaine resulted in more rapid and complete analgesia compared with a control group [99]. Pethidine 50 mg alone did not produce as effective analgesia as pethidine with adrenaline [146, 147]. Alfentanil, however, was unsatisfactory [88].

Intrathecal administration has proved to be much more satisfactory in labour (fig. 1). Excellent analgesia, often lasting several hours, has been reported after morphine 0.5–2 mg given for the first stage of labour, although the effects were much less marked during the second stage [3, 15, 175]. The incidence of side effects, even though classified as “minor”, was distressingly high [3]. It is possible to decrease these with naloxone without affecting the degree of analgesia [29], but this complicates what should be a simple technique. Despite the simplicity and efficacy of using intrathecal opioids in labour, Crawford [56] has warned that the potential for respiratory depression always exists and makes routine use of the technique in obstetrics difficult to accept. Apnoea has now been reported some 7 h after intrathecal morphine 1 mg given to a mother in labour [4].

In view of the high incidence of side effects, intrathecal morphine in labour would best be reserved for those situations in which it is essential to avoid the unwanted effects of local anaesthetics, particularly hypotension, for example in patients with congenital heart disease [5].

**Paediatric use**

There are few reports of the use of spinal opioids in children. Jones and colleagues [98] found that postoperative analgesia lasted more than 24 h in 22 of 56 children given intrathecal morphine before the surgical incision. Fifteen children required additional analgesia at 22 h, while in the remainder pain relief lasted approximately 13 h. The initial 27 children received a dose of 0.03 mg kg\(^{-1}\), but six of these developed respiratory depression an average of 4.4 h after the morphine and required naloxone. The remaining children were given 0.02 mg kg\(^{-1}\) and three of these required naloxone to antagonize respiratory depression.

Extradural morphine behaves in a similar way...
as in adults. A dose of 50 \( \mu \text{g kg}^{-1} \) after abdominal or genito-urinary surgery showed an onset time of 30 min and an average duration of 19.5 h [11]. Complications were also similar, with incidences of pruritis of 20\%, nausea and vomiting of 40\% and urinary retention of 28\%. The ventilatory response to carbon dioxide was depressed after surgery and before morphine, probably as a result of the residual effects of the anaesthetic, but remained low for 22 h, probably because of the extradural morphine. The pharmacokinetic parameters were similar to those in the adult, except for a shorter terminal half-life resulting from the greater total body clearance in children. Extradural sufentanil has also been shown to produce rapid, effective, but short lasting analgesia (mean 198 min) in children [20]. The complications were similar to morphine, but drowsiness was also reported in 67\% of the children. The slope of the carbon dioxide response curve was significantly depressed for up to 60 min, which led the authors to recommend close monitoring for more than 1 h. About 50\% less parenteral narcotic was given to children who received caudal morphine 0.07 mg kg\(^{-1}\) in 5 or 10 ml at the end of cardiac surgery [165]. The caudal morphine was effective after both thoracotomy and sternotomy, although increased sedation was common.

**Other acute pain**

Extradural morphine was an effective method of pain relief in patients with multiple fractured ribs [97, 119], but intrathecal morphine 1.0–2.0 mg did not provide adequate analgesia in 27\% of such patients, and the incidence of complications was high [63]. Extradural methadone 4 mg given before operation facilitated mobilization and easier nursing in patients with proximal femoral fractures [138]. Extradural fentanyl was found to be efficacious, easy to use and a safe alternative to both general anaesthesia and conventional extradural analgesia in patients undergoing extracorporeal shock wave lithotripsy [141].

The pain of acute myocardial infarction has been relieved by both intrathecal [143] and extradural morphine [180]. In both instances pain relief was obtained where the i.m. and i.v. routes had failed. Morphine 2–3 mg given through thoracolumbar catheters on an outpatient basis once or twice a day resulted in a lessening of angina in seven patients who had already undergone coronary artery surgery and in whom other medical treatment was ineffective [49].

Spinally applied opioids are effective in a number of acute painful conditions and this is an area which would benefit from more intensive investigation.
PHARMACOKINETIC ASPECTS
A knowledge of the pharmacokinetic behaviour of
spinally applied opioids will help in the under-
standing of the observed pharmacodynamic ef-
effects, but requires measurement of plasma and
CSF concentrations. The major analgesic effect of
extradural opioids depends on movement of the
drug across the dura and into the spinal cord.
Thus the more fat soluble drugs would be
expected to cross the dura more rapidly, but a
study using an isolated preparation of lumbar and
cranial dura found that lipophilicity was ap-
parently not an important factor because mor-
phine and diamorphine had similar permeabilities
[134]. There was a marked relationship between
the permeability of the compounds tested and
molecular weight with the exception of fentanyl,
which crossed the dura faster than would be
expected. The authors suggested that molecular
shape may be the important factor and that,
whereas most of the compounds they tested had a
shape approximate to a sphere, fentanyl is an
extended molecule. However, the conditions of
the experiment were very artificial and the dura is
not a lipid membrane.

Once in the CSF, the opioid has to diffuse into
the spinal cord in the region of the dorsal horn of
grey matter to exert its effect [204]. In animal
experiments, cats were studied 1–3 h after
intrathecal administration of carbon-14 labelled
morphine. Radioactivity was limited mainly to the
external 1–2 mm of the cord even at the longest
time interval, while only minimal penetration was
seen at the shortest. This would explain the long
latency seen after morphine.

After extradural morphine, peak plasma concen-
trations were reached at approximately 15 min
and the plasma curves were similar to those seen
after i.m. injection [132, 135]. Morphine crossed
the dura slowly, appearing in the CSF in 15 min
with peak concentrations between 90 and 120 min
[135, 179], when the concentrations were about 25
times those in plasma. The half-lives in plasma
and CSF are very similar: 3.5–4 h [134, 135].
Disappearance of morphine from CSF is pro-
longed, 80% still being present 4 h after injection
and about 50% at 12 h [179]. The CSF concen-
tration 24 h after extradural morphine 6 mg
was approximately 16 ng ml⁻¹ [134]. However,
the amount of morphine actually entering the
CSF after extradural injection is small, Nordberg
and colleagues [134] calculating the CSF bio-
availability to be approximately 2.0%, whereas
Sjostrom and colleagues [179] found that the
fraction crossing the dura was 3.6%.

It might be expected that the larger the volume
of the injectate containing the opioid the greater
would be the absorption because of the more
widespread distribution, but this has not proven
to be the case. A volume of 10 or 20 ml did not
influence CSF concentration of morphine [132].
Others found no difference in serum concen-
trations of morphine after 6 mg in 3 ml or in
30 ml, although analgesia lasted somewhat longer
after the larger volume [173]. It has also been
noted that increasing the volume of diluent for
fentanyl 50 µg did not slow onset time and
decrease the duration of effect as expected, but
exactly the reverse [8]. Doubling the volume of
injectate with the same mass of drug had no effect
on the quality or duration of analgesia [149].

Diamorphine, the diacetyl derivative of mor-
phine, is much more fat soluble and clinically has
a more rapid onset and shorter duration of effect
than morphine. In the blood stream it is rapidly
decacylated to morphine, but this occurs only
very slowly in CSF. Thus an indication of its
systemic absorption can be obtained by measuring
the plasma concentration of morphine. Watson
and colleagues [194] found that peak plasma
concentrations after extradural diamorphine
5.5 mg occurred significantly faster, and were
significantly higher, than after morphine 5.0 mg.
They estimated the fraction of diamorphine
crossing the dura to be 55% that of morphine.

Pethidine is also more fat soluble than morphine
and has a faster onset and shorter duration of action.
Peak CSF concentrations occurred at
15–30 min, but the fraction crossing the dura was
the same as for morphine [179]. It disappeared
from the CSF about four times faster than
morphine [179].

After intrathecal morphine 2.5 mg given before
cardiopulmonary bypass, CSF concentrations de-
creased rapidly for 10 min and then reached a
plateau at 10 µmol litre⁻¹ [126]. After dia-
morphine 2.0 mg, the concentrations decreased
rapidly initially and continued to decrease during
the 25-min study period, thus indicating that
diamorphine is removed more rapidly from the
CSF. This conclusion was confirmed by the work
of Kotob and colleagues [104], who measured
plasma and CSF concentrations for 6 h after 1 mg
of intrathecal morphine or diamorphine. After
morphine, peak plasma concentrations were sig-
nificantly lower, and peaked significantly later, than after diamorphine. The mean elimination half-life of diamorphine from CSF was 43 min compared with 73 min for morphine.

Apart from passing out of intervertebral foramina, there are three possible fates for drug injected into the extradural space, namely vascular absorption, dissolving in extradural fat or dural transfer. It is possible to influence the first of these by inclusion of a vasoconstrictor in the injectate. Adrenaline, however, did not influence plasma or CSF concentrations of morphine, or the duration of analgesia after extradural injection [136]. In contrast, addition of adrenaline to diamorphine significantly decreased plasma concentrations of morphine by decreasing systemic absorption by over 50%, and also prolonged the duration of analgesia [95].

The available pharmacokinetic data explain the pharmacodynamic effects of spinal opioids. They have demonstrated the slow dural transfer of morphine and its prolonged presence in the CSF, thus correlating with its slow onset and long duration of action, and high incidence of side effects. They have also demonstrated that the more fat soluble drugs enter the circulation more rapidly and also leave the CSF more rapidly than morphine; thus less is available for rostral spread in the CSF and side effects should be fewer.

**COMPARISON OF TECHNIQUES**

**Intrathecal with Extradural**

Nordberg [133] has commented that the extent to which the extradural route is preferred to the intrathecal is rather surprising. Apart from the fact that an intrathecal injection is technically easier, there are good arguments for considering it the more logical. The main determinant of spinal analgesia is the CSF concentration of the opioid. Direct intrathecal injection avoids the problem of systemic absorption and the possibility of the drug dissolving in the extradural fat, both of which compete with dural transfer of the drug. Peak CSF concentrations of morphine occur 1–2 h after extradural injection. The CSF bioavailability of extradural morphine is about 2.0% [134] and an intrathecal dose of 0.2 mg would produce CSF concentrations similar to those resulting from the injection of 10 mg to the extradural space. Furthermore, a single injection produces prolonged analgesia.

There have been no double-blind controlled trials comparing the two methods of administration. The intrathecal route has been reported as being superior to the extradural [16], but as the doses of the drugs (morphine 2.0 mg, diamorphine 0.5 mg) were the same by both routes, this is not surprising. A retrospective study [77] revealed that after thoracotomy there was no difference in the quality of analgesia between extradural and intrathecal morphine, but that this was of longer duration and achieved with a much smaller dose of drug after intrathecal injection.

The reason for anaesthetists preferring the extradural route is that the incidence of complications, both minor [3, 93] and major [60, 79, 87, 152], is much greater after intrathecal use.

**Spinal Opioids Compared with Existing Techniques**

Extradural and intrathecal injections require skill to perform, have a documented failure rate (particularly thoracic extradural) and may be associated with serious complications and even death. It is possible, with attention to detail, to produce adequate postoperative pain relief by much simpler methods using i.m. [12] or i.v. injection, or even regular sublingual administration [33]. In view of this, the risk:benefit ratio of spinal opioids must be carefully balanced and it is essential that this new technique be shown to offer significant advantages over existing methods of pain relief.

Many of the initial reports of spinal opioids were nothing short of spectacular, with claims of minimal doses of drug producing very prolonged analgesia and virtually no complications. Unfortunately, these reports failed to adhere to the basic principles of clinical evaluation of new techniques and it was impossible to eliminate bias from the observations. In order to obtain a valid comparison with conventional methods of analgesia a number of steps must be followed. First, there must be an acceptable method of evaluation of pain relief. This might involve subjective assessment on pain scales, a visual linear analogue, or a more objective method such as measurement of respiratory function when relevant to the surgery performed. The number of demands for additional analgesia from a patient controlled device is also acceptable, but the number of i.m. injections given at the discretion of a nurse is not; even in the best units, the latter would only give some indication as to the duration of analgesia,
not its quality. Second, allocation to the two treatment groups must be randomized. Third, to eliminate bias, each patient must receive an extradural or intrathecal injection and each must receive either placebo or drug by the other route of administration. Fourth, again to eliminate bias, all medications must be given on a double-blind basis. Fifth, the groups must be comparable in terms of the origin and severity of the pain to be treated.

To perform such a trial is time consuming, administratively difficult and could also be questioned from an ethical point of view. It is also necessary to use equipotent doses of the drug, but information on relative potencies is not available when comparing spinal and systemic administration. For instance, there is a marked difference between the systemic and extradural potencies of pethidine and morphine [178]. Even the best controlled trials can be beset with problems. Thus in a cross-over trial comparing extradural pethidine 50 mg with 100 mg given i.m. and extradural bupivacaine after lower abdominal surgery, the former was shown to be superior [31]. However, the distribution of treatments was such that many more patients received extradural pethidine as their third and fourth treatments, and intensity of pain diminishes as time passes after surgery.

Jacobson and colleagues [94] found no significant difference in the quality of analgesia when diamorphine 0.1 mg kg\(^{-1}\) was compared by the extradural or i.m. routes, although duration of effect was longer in the former group. Extradural morphine 5 mg produced a longer period of analgesia than 10 mg given i.m., but otherwise there was no great difference between the two [40]. In grossly obese patients, there was no significant difference in the quality of analgesia produced by morphine 0.1 mg kg\(^{-1}\) i.m. or 4 mg given extradurally, but morphine consumption was much greater after i.m. injection, being a mean of 1.8 mg h\(^{-1}\) over 36 h compared with 0.26 mg h\(^{-1}\) [156]. Using a patient controlled analgesia system for i.v. and extradural fentanyl, no significant difference in overall pain relief was found by subjective or objective measurements [74].

Other workers have found the extradural route superior. Extradural diamorphine was found to produce more prolonged and intense analgesia than the same dose given i.m. [116]. Malins and colleagues [120] found thoracic extradural diamorphine 5 mg superior to the i.m. route and could not agree with Jacobson and colleagues [94] that i.m. diamorphine could exert an effect for so long after thoracotomy. Fentanyl 200 \(\mu\)g given into the extradural space produced more effective analgesia than 200 \(\mu\)g i.m., although this effect was apparent only for 60 min [112].

There is no conclusive evidence that opioids injected extradurally or intrathecally provide analgesia superior to that produced with other routes of administration. An undisputed advantage, however, is their ability to produce more prolonged analgesia at much smaller doses. Extradural morphine produces long lasting analgesia with doses that are only 20–40% of the normal i.v. dose; 8% of such doses are effective when given intrathecally [59]. Thus patients could be expected to be less drowsy, more co-operative and more mobile, with all the attendant advantages.

### SIDE EFFECTS

Acceptance of a new technique depends not only on its efficacy, but also on the nature and incidence of side effects. The latter occur frequently after extradural and intrathecal opioids, and although many are regarded as being “minor”, they can nevertheless be very annoying to the patient. Typical incidences are shown in table IV, although the frequencies of those mentioned vary from zero to almost 100% in individual reports.

#### Minor Sequelae

**Nausea and vomiting**

This side effect cannot be divorced from the use of opioids. In volunteers, Bromage and colleagues [28] observed nausea and vomiting about 6 h after extradural morphine in all subjects. In general, the incidence appears to be greater after intrathecal injection, but it should be remembered that there is a 30% incidence after parenteral use of opioids [54].

<table>
<thead>
<tr>
<th></th>
<th>Extradural [202]</th>
<th>Intrathecal [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritis</td>
<td>41%</td>
<td>80%</td>
</tr>
<tr>
<td>Nausea</td>
<td>48%</td>
<td>53%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
<td>43%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>34%</td>
<td>43%</td>
</tr>
</tbody>
</table>
Pruritis

The reported incidence of this annoying side effect varies considerably and has been reported as occurring in 100% of volunteers given extradural morphine 10 mg [27]. In one series, up to 67% of patients developed pruritis after morphine, the incidence being unrelated to the dose [121]. This contrasts with the report of Lanz, Kehrberger and Theiss [106], who found that the incidence of pruritis after extradural morphine increased from 17% after 1.0 mg to 56% after 5 mg. Pruritis on the face and trunk began 3–5 h after intrathecal morphine 0.5–1.0 mg and lasted for up to 30 h [3]. It has also been reported after extradural fentanyl and diamorphine, but there are virtually no data comparing the drugs.

The itching is not confined to the segmental area of action of the opioid, but also occurs around the head and neck. The mechanism is not known, but it is unlikely to be the result of histamine release because there is no other evidence of such a reaction and it occurs with fentanyl, which does not release histamine. Korsch and colleagues [103] did not find increased plasma histamine concentrations in patients who complained of pruritis after extradural morphine 5 mg, and the concentrations during the maximum period of itching did not differ from those who had received i.m. pethidine. Although there is no generalized histamine release, this does not rule out local tissue release of histamine. The overall incidence after extradural morphine is about 10% and it is severe in about 1% [152]. After extradural pethidine, Brownridge [30] noted that about 33% of 2000 patients complained of itching, but usually only on direct questioning, and that the symptom usually diminished with subsequent doses. In only one of these patients was the pruritis severe. The original belief that the pruritis was caused by the preservative in the injectate has been discounted. The pruritis can be antagonized with naloxone [29].

Urinary retention

This has been described as the most troublesome complication of extradural opioids [152], and an incidence of 90% or more can be expected in young males receiving extradural morphine 10 mg [26]. In the reported clinical series the incidence varies widely. Torda and Pybus [186] noted that only one of 24 patients required catheterization, but in other series frequencies of 22% [158] and 39% [108] have been reported. Urinary retention occurred in 79% of patients undergoing ano-rectal surgery [86].

Rawal and colleagues [154] studied the urodynamic effects of extradural morphine 2, 4 and 10 mg and of morphine 10 mg i.m. They found that, irrespective of dose, extradural morphine resulted in a marked relaxation of the detrusor muscle shortly after injection, with a corresponding increase in maximal bladder capacity leading to urinary retention. This lasted an average of 14–16 h. Only minimal effects were seen after i.m. or i.v. injection. The duration of effect was not dose related. The rapid onset and the absence of effects after parenteral administration favour a spinal action and may result from interference with sacral parasympathetic outflow. There may possibly be opioid receptors in the urinary bladder. All these effects were antagonized promptly by naloxone 0.8 mg i.v.

All these “minor” side effects have also been reported in children, with similar frequency [11, 20]. They also occur more often after intrathecal than after extradural injection (table IV).

Serious Sequelae

Neurological damage

The possibility of permanent neurological damage after any extradural or intrathecal procedure is always cause for concern. Permanent neurological sequelae have not been a problem, although one case of meningitis has been reported after long-term treatment [9].

Preparations containing preservatives should not be used, as some of these are known to be neurotoxic, for example chlorocresol. Problems have occurred in a patient receiving long term extradural morphine therapy for intractable pain [71]. Originally a preservative free preparation was used, but this was changed to a generic product for cost reasons. This caused a burning pain on injection, with less satisfactory analgesia. An extradurogram showed non-specific areas of flow restriction. The generic formulation contained phenol 2.5 mg and formaldehyde 2.8 mg with morphine 15 mg and it was calculated that the patient had received phenol 30 mg and formaldehyde 33.6 mg during therapy with this preparation. Satisfactory pain relief was re-instated after return to preservative free morphine.

It is unlikely that any of the opioids which have
been used extradurally or intrathecally cause neurological damage.

Respiratory depression

The specific advantage that it was most hoped would be gained from the use of spinally applied opioids, namely absence of respiratory depression, has not been obtained. The literature now abounds with case reports of this complication, the most sinister aspect of which is its delayed appearance. After intrathecal opioids, respiratory depression develops 6-11 h after administration and may last for as long as 23 h [60]. After extradural opioids, respiratory depression can occur within 1 h, and in just a few minutes with the more fat soluble drugs [23, 192], although most instances have been delayed for 4-6 h. A delay of 16.5 h has been reported [202]. Morphine is almost invariably the drug involved.

Studies in both volunteers and patients have consistently shown significant and prolonged respiratory depression after extradural morphine. Maximum depression of the carbon dioxide response curve was found between 6 and 10 h after extradural morphine 10 mg in volunteers and there was still evidence of depression 22 h after injection [36]. Similar results were found by Knill, Clement and Thompson [102] who found that the end-tidal carbon dioxide concentration was still increased and the slope of the carbon dioxide response curve was still slightly depressed 24 h after extradural morphine 3.5 mg. Measurement of airway occlusion pressure responses to carbon dioxide were depressed after extradural morphine 10 mg in young patients after abdominal surgery, indicating a decreased respiratory drive, but there was a high degree of individual variability in the magnitude and course of this effect [64]. Rawal and Wattwil [159] found a dose related depression of the response to carbon dioxide, while Madsen and colleagues [118] recorded a significantly increased Pa\textsubscript{CO\textsubscript{2}} 20 h after extradural morphine 8 mg. Prolonged ventilatory depression has also been reported in children [11]. Maximum depression of minute ventilation occurred 1–2 h after injection of extradural morphine 0.1 mg kg\textsuperscript{-1} in patients with chronic back pain [100]. The authors proposed that this was a result of vascular absorption of the drug and distribution to the brain, but they also found a late depression of the response at 8 h, which corresponded with the maximal rise in the segmental level of analgesia and loss of skin temperature discrimination. There was considerable variation in the magnitude of this late displacement.

A respiratory inductance plethysmograph has been used to study respiratory pattern after extradural or i.v. morphine given after thoracotomy [171]. Morphine 5 mg was given extradurally approximately 1 h before the end of surgery and further 5-mg doses were given when necessary. The results were compared with those for i.v. morphine given in a double-blind manner, and are shown in figure 2. Periods of hypopnoea/apnoea or slow rates of ventilation were seen in six of eight patients given extradural morphine, but in only one of the i.v. group. The authors commented that the alterations in respiratory pattern were subtle and insidious in onset and unpredictable in duration, and the fact that no patient required naloxone or artificial ventilation should not detract from the inherent dangers of postoperative use of extradural morphine. They stressed that hourly monitoring of ventilatory rate could be quite misleading.

The explanation of the delayed respiratory depression lies in the pharmacokinetic properties of morphine. Being poorly lipid soluble, it enters the spinal cord slowly and its disappearance from the CSF is prolonged [179]. It therefore remains in the CSF and slowly migrates cephalad. Observations on the circulation of CSF have shown that it takes 1–2 h to reach the cisterna magna from the lumbar region and 4–8 h to pass through the foramina of Luschka and Magendie to the fourth ventricle [62]. Experimental work in primates found that intrathecal morphine was maximally concentrated in the medulla at 6 h [85]. Any factors that accelerate the movement of morphine in the CSF will result in a more rapid appearance of, and perhaps a more profound, respiratory depression [100]. These latter authors reported a patient who experienced coughing 3 h after extradural morphine 0.1 mg kg\textsuperscript{-1}, which resulted in a rapid rise in segmental analgesia, to include the mandibular and maxillary divisions of the trigeminal nerve by 4 h. This was accompanied by severe respiratory depression.

Incidence

The true incidence of respiratory depression will be known only when the results of large series, of which there have been very few, are available. The largest numbers come from two reports from Sweden (table V). In the first of these [87], respiratory depression occurred after
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extradural morphine 2.0–4.0 mg in 0.25–0.4% of patients. In the second [153], morphine (usually 4 mg) was used in 96% of patients and the incidence of respiratory depression decreased to 0.09%. Both reports noted a much higher frequency of respiratory depression after intrathecal morphine.

The findings of these Swedish workers are not in accord with those of others who use morphine. Thus respiratory depression occurred in four of...
TABLE VI. Respiratory depression after extradural opioids other than morphine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time of occurrence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamorphine</td>
<td>2-10 mg</td>
<td>20 min–4.5 h</td>
<td>[53, 137, 194]</td>
</tr>
<tr>
<td>Pethidine</td>
<td>50–100 mg</td>
<td>5–30 min</td>
<td>[32, 174]</td>
</tr>
<tr>
<td>Methadone</td>
<td>4–6 mg</td>
<td>20 min–4 h</td>
<td>[196, 197]</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1 mg</td>
<td>4.5 h</td>
<td>[203]</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>50 μg</td>
<td>5–15 min</td>
<td>[23, 192]</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 μg</td>
<td>30 min, 4 h</td>
<td>[142, 199]</td>
</tr>
</tbody>
</table>

623 patients (1 in 156, 0.6%) reported by Ready and colleagues [160] and four of 128 (1 in 32, 3.1%) in a Canadian multicentre trial [202]. In another large series [181], the incidence of respiratory depression was 0.9% in patients who received morphine 4–6 mg with a tendency for more frequent occurrence after thoracic extradural injection. Apart from isolated case reports, many studies investigating the analgesic effects of extradural and intrathecal morphine, and containing relatively few patients, have reported instances of respiratory depression, occasionally with alarming frequency. Thus three of six patients given morphine 1.0 mg intrathecally developed profound, delayed respiratory depression [60]. After morphine 5 mg by the thoracic route, eight of 30 patients gradually lost consciousness with respiratory depression 30–73 min after the injection, the general anaesthetic having contained no opioid analgesic [72].

It should be noted that the Swedish studies were retrospective, which have several problems of data retrieval. Also, many of the patients were being treated for chronic pain conditions and these patients are known to be resistant to the respiratory depressant effects of opioids [54].

Respiratory depression can also follow use of the more fat soluble opioids (table VI). When occurring soon after injection it can be ascribed to systemic absorption. Scott and McLure [174] reported two patients who developed severe depression within 30 min of extradural pethidine 50 mg, while Brownridge, Wrobel and Watt-Smith [32] reported a patient who became increasingly drowsy with gasping ventilation after pethidine 50 mg given into a catheter that was accidentally placed intrathecally. It is pertinent to note with regard to this case that the nurse had actually left the patient’s room, but fortunately the husband drew attention to the problem. Extradural sufentanil has been followed within a few minutes by respiratory depression [23, 192]. Three of 12 patients given extradural diamorphine 5.5 mg had ventilatory rates of less than 8 b.p.m. between 20 and 90 min later [194], while all patients given 10 mg into the thoracic space had evidence of respiratory depression some 2 h later [137].

There may possibly be an association between the appearance of respiratory depression after extradural administration which has been complicated by previous dural puncture [53, 196]. Radiological evidence exists of injectate into the extradural space passing through a previous accidental dural puncture hole into the subarachnoid space [110].

More sinister delayed respiratory depression can also occur. Extradural diamorphine 3 mg resulted in apnoea at 4.5 h in a patient who had also had a spinal anaesthetic [53]. Respiratory depression occurred 4 h after lumbar extradural methadone given after thoracic surgery [197]. Hydromorphone 1.0 mg, which is much more fat soluble than morphine, caused apnoea 4.5 h later in a patient who had not received any other opioid in the previous 10 h [203].

Theoretically, respiratory depression should occur less frequently with the more fat soluble opioids as they will enter the spinal cord more rapidly and will not remain in the CSF. There are far fewer cases reported, but the frequency of use of these agents compared with morphine is not known. Few experimental studies have been performed. Diamorphine 5 mg either i.m. or into the thoracic extradural space depressed respiration maximally within 30 min of injection and, although statistically significant, its clinical importance was slight [120]. Ahuja and Strunin [6] investigated the respiratory effects of a bolus injection of fentanyl 1.5 μg kg⁻¹ followed by a continuous infusion into the thoracic extradural space. The bolus injection resulted in a significant decrease in rate of ventilation and a non-significant increase in end-tidal carbon dioxide.
concentration within minutes, which was similar to the findings of others [112]. The changes were accentuated by prior parenteral administration of morphine. A continuous infusion of fentanyl 50–100 μg h⁻¹ commenced 1 h after the bolus injection and continued for 18 h had no further effect on the end-tidal carbon dioxide concentration or ventilatory rate, despite a gradually increasing plasma concentration of fentanyl.

Molke-Jensen and colleagues [123] were disappointed to find that the very fat soluble buprenorphine in an extradural dose of 0.15 mg produced prolonged and biphasic depression of the carbon dioxide response, with respiratory depression being significant between 2 and 4 h and again at 8–10 h. No clinical reports of respiratory depression after the drug have yet been reported. The mixed agonist–antagonist butorphanol 2–4 mg given extradurally depressed the ventilatory response to carbon dioxide for 12 h [2].

Thus all the narcotic analgesics have the propensity to produce respiratory depression, but there is no doubt that it is more common after morphine. Fentanyl may be the least problematic, although the frequency of its use is not known. Profound central nervous system and respiratory depression has followed just over 1 h after 100 μg given extradurally, but the patient had also received i.v. midazolam, droperidol and nalbuphine to counteract pruritis [199]. An infusion of naloxone was necessary to maintain respiration. Respiratory depression has been reported 4 h after fentanyl 100 μg with adrenaline, the definition of respiratory depression being a rate of ventilation less than 10 b.p.m. or a venous carbon dioxide partial pressure more than 1.33 kPa greater than control [142]. The rate of ventilation in this patient was 16 and the venous $PCO_2$ 1.47 kPa greater than control. This occurred in one of two patients given this dose of fentanyl and hardly justifies the claim of a 50% incidence of respiratory depression with this drug [152].

**Predisposing factors**

The factors that may predispose to the development of respiratory depression are shown in table VII. Most patients are elderly, 77% in the recent nationwide survey in Sweden being older than 65 yr. It is in these elderly patients, who frequently have concomitant cardiopulmonary disease, that good analgesia with minimal central depression is so often required. Nevertheless, profound respiratory depression can occur in the young [60, 203]. The water soluble drug morphine has been most frequently implicated, although it does occur with the more lipophilic drugs (table V).

The residual effects of other central depressants are frequently quoted as being contributory to the respiratory depression produced by spinal opioids. Severe respiratory depression, resistant to naloxone, but antagonized with physostigmine, has been reported in a patient who received droperidol 1.25 mg i.v. for nausea after delivery, followed later by extradural hydromorphone 1.25 mg [50]. Lack of tolerance to opioids is another important factor and there does not appear to be a problem, even when very large doses are given extradurally to patients with intractable pain who have usually received large doses of a variety of drugs for some time [9]. The respiratory depressant effects of extradural morphine can be seen 16 h or more after administration [36] and further depressant drugs, by any route, at this time may result in significant respiratory depression.

Increased intrathoracic pressures, caused by artificial ventilation, coughing or the grunting respiration associated with pain may serve to accelerate passage of drug containing CSF cephalad. This is well illustrated in the case reported by Kafer and her colleagues [100]. The incidence is more common after intrathecal opioids [87, 153] and, although it has been reported after extradural administration after accidental dural puncture [53, 196], the number of such cases is too few to draw any firm conclusions. The large doses of morphine (10 mg) that may be required to produce satisfactory analgesia after upper abdominal surgery are associated with a higher incidence of respiratory depression than 2–4 mg [159]. It is also more common after intrathecal doses greater than 1 mg [79, 93]. The thoracic...
extradural approach also is associated with a higher reported incidence [87, 181].

A wide spectrum of factors are involved in the development of this complication, so much so that the most predictable thing that can be said about its appearance is that it is unpredictable. This has important implications for the management of patients who have received spinal opioids.

**Prevention**

It has been suggested that patients receiving spinal opioids should be nursed in the semi-sitting position, in the hope of preventing respiratory depression. It has been suggested that intrathecal opioids should be used in hyperbaric solution [170], but supporting evidence for these views has not been forthcoming. Respiratory depression has followed hyperbaric morphine 1.0 mg in a patient kept in the head-up position [4]. McCaughhey and Graham [113] found a consistent pattern of respiratory depression after extradural morphine 2 mg in patients kept supine. In the sitting position the same degree of respiratory depression was not observed, although there was considerable individual variation. Others have found that the 45° elevated position offered no protection with regard to the incidence or degree of respiratory depression after lumbar extradural morphine 4 mg [124]. The head down position should be avoided. Severe respiratory depression has occurred after only 0.4 mg of hyperbaric morphine given intrathecally in such circumstance [80].

Naloxone antagonizes all the unwanted effects of spinal opioids, although repeated doses may be necessary to maintain adequate ventilation. Analgesia is not usually affected, and this has led to attempts to reduce the incidence of side effects by concomitant administration of naloxone. Thind, Wells and Wilkes [184] found that naloxone 2 mg given by infusion over 12 h after extradural morphine 4 mg did not affect analgesia and reduced the severity, but not the incidence of side effects. There was no respiratory depression. Rawal and colleagues [155] used 5 and 10 μg kg⁻¹ h⁻¹ after extradural morphine 4 mg and found that the larger dose decreased the duration of analgesia by about 25%. The naloxone also reduced the incidence of side effects and a dose related stimulatory effect on ventilation was seen.

These findings are contrary to those of Gowan and colleagues [84], who used three bolus doses and infusion rates of naloxone in patients given extradural morphine 0.1 mg kg⁻¹. There was a trend towards decreased analgesia with all three rates of infusion of naloxone and side effects occurred in all groups. They concluded that a naloxone infusion was not an appropriate technique for reducing side effects while maintaining analgesia after extradural morphine.

The partial opioid agonist nalbuphine also has been used to prevent respiratory depression [68]. A bolus dose of 0.2 mg followed by an infusion of 0.05 mg kg⁻¹ h⁻¹ resulted in lower arterial carbon dioxide tensions than in a control group. Naloxone was required in the latter patients. The results of giving a partial agonist in the presence of an agonist may be additive or antagonistic, depending on the relative concentrations of two drugs [35], and it would be wiser to avoid such a drug combination.

**FEASIBILITY OF USE OF SPINAL OPIOIDS FOR POSTOPERATIVE PAIN RELIEF**

Intrathecal and extradural opioids produce excellent analgesia with much smaller doses of drug than is achieved via other routes. There is therefore less central depression and greater patient mobility and co-operation, with all the attendant benefits. A major advantage over extradural local anaesthetics is the lack of autonomic block and absence of hypotension. However, there is no doubt that their use is associated with a high incidence of complications, the most sinister of which is delayed respiratory depression.

The proposition of a single injection given at the time of surgery and providing long lasting analgesia is very attractive. A single intrathecal injection of morphine has been shown to be beneficial to patients undergoing abdominal aortic and coronary artery surgery. Significantly less parenteral analgesia is required after operation, the time spent in the intensive care unit is shortened [92] and significantly less hypotensive agents are required after cardiac surgery [190]. However, these types of patient are nursed in an intensive care unit and their lungs are usually ventilated artificially after operation. It would certainly be feasible to perform a single intrathecal injection for the majority of patients undergoing surgery, but repeat administration in the post-operative period would not be possible, there being few anaesthetists prepared to maintain a catheter in the subarachnoid space for several days. Performing an extradural injection is technically more difficult, is more time consuming and
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would not be a feasible proposition for as many patients. An extradural injection does have the advantage that catheter techniques are routinely practised, so that top up doses or continuous infusions are perfectly feasible. The incidence of complications is also lower after extradural opioids than intrathecal.

The biggest constraint on the use of spinal opioids is the nature and incidence of the associated complications. Pruritis, nausea and vomiting and urinary retention are common. The last of these is probably the most troublesome complication and must be taken into account when considering the technique for postoperative analgesia in the majority of patients who will not routinely have urinary catheters. However, the most serious problem is respiratory depression. Although more common after morphine, it does occur after other drugs and it is the unpredictability of its appearance that makes it so dangerous. Large comparative series have not been performed to indicate the frequency of occurrence with the different opioids.

Because of the problem of respiratory depression, the majority of workers recommend that these patients be kept in areas where there is a higher degree of surveillance than can be provided on an ordinary ward, and for up to 24 h after the last injection, certainly with morphine. Some form of respiratory monitoring is mandatory and probably most easily provided by the constant supervision of the nursing staff. Respiratory inductance plethysmography is not practical as a routine, and although apnoea alarms have been used [7], apnoea is the very problem that it is hoped to prevent. End-tidal carbon dioxide measurements can be valuable, while transcutaneous carbon dioxide electrodes still await critical analysis in a large series of patients. Pulse oximetry may also prove useful, but choosing the correct saturation below which intervention becomes necessary will depend on the individual patient. Respiratory depression usually comes on gradually, often indicated by a slowing of the rate of ventilation [181], and it is the trend indicated by the respiratory monitoring equipment that must be taken into account. Hourly monitoring of ventilatory rate is totally unacceptable. Use of continuous infusions of naloxone, although successful in reducing the severity of complications (but possibly also analgesic efficacy [84]), adds to the complexity of the procedure and mitigates against widespread use of the method.

In a nationwide survey in Sweden [153], it was reported that 33% of anaesthetic departments kept patients under close surveillance in an intensive care unit for 12–24 h after extradural morphine, 40% kept the patients under close surveillance for up to 12 h, and 18% returned the patients to an ordinary ward with no special observations. The incidence of respiratory depression in this survey was 0.09%, which is considerably lower than that reported by others with reasonably large series (table VI).

Recently, the development of an Acute Pain Service for the management of postoperative pain has been described. This allows use of patient controlled analgesia and extradural opioids in general wards as well as in areas of close surveillance [160]. Others have also described their experiences of using extradural opioids on general surgical and medical wards [34]. Ready and colleagues [160] stressed both that the service must be available on a 24-h basis, and the importance of a joint educational programme with the nursing staff. Standard procedures are issued, the nurses give the opioid (usually morphine) through the extradural catheter and have instructions on the treatment of complications. Criteria are laid down for the use of mechanical respiratory monitors, and for the circumstances in which they are not to be used. Both groups require naloxone to be immediately available.

Bursch and Stedman [34] have used this approach since 1984. They analysed retrospectively data from 125 patients and reported a low incidence of complications and no respiratory depression. Because the analysis was retrospective, they were unable to comment on the quality of analgesia. Ready and colleagues [160] reported that, after 18 months of operation, their service continues to grow and is popular with patients and surgeons. Extraludrs have been used in 623 patients. Delayed respiratory depression occurred in four, all of whom were high risk patients who had undergone prolonged surgery and who were being cared for in an intensive care unit.

The policy of how and where to manage patients who are in receipt of spinal opioids must rest with individual anaesthetists and their departments. The programmes mentioned above are time consuming and require much manpower. It is difficult to see, given the facilities that exist in the U.K. at the moment and the commitments of nursing and medical staff, how such patients can be safely managed on an ordinary ward. The
The spectrum of occurrence of respiratory depression after extradural opioids is wide [203] and close surveillance is necessary for up to 24 h after administration. It is therefore difficult to justify returning these patients directly to an ordinary ward.

**THE FUTURE**

The introduction of spinal opioids has been an exciting and significant advance in the management of acute and chronic pain. The incidence of side effects, however, is high. Morphine is still the drug most commonly used worldwide, but the more fat soluble opioids are more popular in the U.K., although exact figures are not available. The search will continue for drugs with a more specific analgesic action at cord level, in the hope of removing the possibility of respiratory depression. Midazolam has been used extradurally [163] and intrathecally [83] and is effective in relieving somatic, but not visceral pain. Perhaps the analgesic actions of benzodiazepines can be developed without associated central effects.

Endogenous peptides have been used and prolonged analgesia has been reported after intrathecal β-endorphin [140]. An infusion of somatostatin after a 250-μg bolus provided complete analgesia after surgery and was not influenced by the administration of naloxone [46]. Modification of endogenous peptides might be possible and result in compounds with long lasting analgesic properties. Calcitonin has produced prolonged analgesia when injected intrathecally in patients with intractable pain [75] and was associated with significantly less postoperative pain when given together with lignocaine intrathecally for spinal analgesia [122]. The manufacturers of salmon calcitonin, however, have warned of its possible serious effects when used in this way [176]. For long term use in patients with intractable pain, drug combinations with the α₂-agonist clonidine or the synthetic opioid D-ala, D-leu-enkephalin (DADL) may help in those developing tolerance to opioids [52]. Droperidol has been used extradurally for this purpose, with benefit [13].

The future will also see more use of patient controlled analgesia given by the extradural route and the development of sophisticated infusion pumps for long term self-administration of opioids. Above all, what are needed are extensive, controlled, comparative trials to identify the most suitable drug for use in acute pain and the development of guidelines so that the technique can be extended to the majority of patients undergoing surgery.

**RATIONAL USE OF EXTRADURAL AND INTRATHERCAL OPIOIDS**

The pharmacokinetic and pharmacodynamic effects of spinal opioids have been extensively investigated, but more work is necessary before the chapter can be finally closed on this new technique of analgesia. From the knowledge that exists at the moment, it is possible to suggest recommendations for their logical use in the management of acute pain.

*Choice of drug.* Morphine has been the most widely used and studied drug and, although its use has been defended [152], the incidence of complications are such that its routine use is difficult to accept. The lipophilic drugs are a much more logical choice, but large trials are necessary to identify the drug of choice.

*Choice of dose.* There is a wide variation in individual susceptibility to opioids and consequently in dose requirements. It is not logical to give a fixed dose to everyone, as has been done for many years with i.m. opioids with totally inadequate results. The dose should be titrated against the patient’s needs and more use should be made of patient controlled analgesia. It is possible, however, to achieve adequate analgesia more easily with spinal opioids by giving a fixed dose of drug, but this does not allow for the patient whose needs are greater than average.

*Choice of route of administration.* Although it is more logical to use the intrathecal route, the logistical problems of giving repeat injections and in particular the high incidence of complications, do not make this the route of choice. Arguments have been made for routinely using the lumbar extradural route even after upper abdominal and thoracic surgery. Adequate analgesia does occur with morphine, and the incidence of respiratory depression is probably lower, but it is slow in onset, which might result in repeated doses being given in belief that the original dose was too small to be effective. With the lipophilic opioids, theoretical considerations would suggest that they should be given at the appropriate spinal level. Studies are required to confirm or refute this hypothesis.

*Precautions and surveillance.* Because of the complications, the degree of surveillance that is
USE OF INTRATHecal AND EXTRADURAL OPIOIDS

required cannot be provided on an ordinary ward. At the moment, close observation is recommended for 24 h, especially after morphine, although this period might safely be shortened for other drugs once information becomes available. It is imperative that nursing staff and resident medical staff be educated in their use, are instructed on the treatment of complications and are able to recognize the circumstances when urgent administration of naloxone is required.

Extradural and intrathecal opioids have been widely accepted by anaesthetists and have proved to be a valuable asset in the management of all types of pain. It would be a pity if one publicized disaster were to set back the technique by 20 years.

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