

# LOCAL ANAESTHETICS AND EPIDURALS

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Local anaesthetics are amazing drugs. Injected into tissue, around a nerve or for a regional block they produce reversible block. An old advertisement from a travelling dentist (1920s) says "Teeth carefully extracted - Adults, 6d each - With Cocaine 6d extra". The moral for acute pain is that local anaesthesia is a luxury rather than a necessity. At least that was the moral. The ground is now shifting. Asking radical questions about acute postoperative management such as "Why are all operations not ambulatory, pain-free and risk-free?", or, more familiar, "Why is this patient still in hospital?", is forcing a reconsideration of the role of combined (local or regional plus general anaesthesia) approaches. Instead of asking questions such as "Is regional better than general anaesthesia" we need to look at the whole episode, before, during and after surgery, not just the operative period. Henrik Kehlet, the Danish surgeon, has been the major force provoking these ideas, refreshingly from professional rather than cost-cutting motives [1, 2]. Costs of each care episode should, however, fall if the hospital stay is reduced, and a healthy patient returned home will cost the community less than a sick patient requiring considerable input from the primary care team. These issues are relevant to this Chapter because the radical changes depend on the use of nerve blocks or regional techniques using local anaesthetics.

Another Scandinavian pioneer, Staffan Arnér from Stockholm, has tackled one of the conundrums of local anaesthetic use in chronic pain, which is why pain relief from local anaesthetics can far outlast the duration of action of the local anaesthetic [3].

This chapter will discuss these important aspects of local anaesthetics, and also will cover epidural use of opioids alone and in combination with local anaesthetics. The aim is not to cover the mechanics of particular

blocks, which is done well in a variety of books, but rather to look into the crystal ball - which areas does current evidence tell us about using local anaesthetics more, and which areas need greater research focus.

## **Acute Pain**

### **A simple operation**

The first example is of a common operation, inguinal hernia repair, which can be done under local anaesthetic alone. Outcomes which need to be considered include the choice of anaesthesia and analgesia, post-herniorrhaphy pain and convalescence, postoperative morbidity (predominantly urinary retention) and choice of surgical technique and recurrence rate. In a randomized double-blind double-dummy study [4] of 200 men Nehra and colleagues compared 0.5% bupivacaine ilioinguinal field block plus oral papaveretum-aspirin tablets with bupivacaine plus oral placebo, saline plus papaveretum-aspirin or saline plus oral placebo to assess pain relief after hernia surgery. Patients were prescribed postoperative opioids to be given on demand. Pain levels and mobility were assessed six and 24 hours after operation. The combination of bupivacaine plus papaveretum-aspirin provided the best results, producing (not surprisingly) significantly less pain, and requiring less additional opioid and with better mobility than saline plus oral placebo. A similar trial nearly twenty years ago [5] randomised 103 patients to either local or general anaesthesia; those patients having local anaesthesia were able to walk, eat, and pass urine significantly earlier than those having general anaesthesia, who experienced more nausea, vomiting, sore throat, and headache.

An audit of inguinal hernia repair under local anaesthesia in an ambulatory set-up provides confirmation that these results may be generalised. Prospective data was collected from 400 consecutive elective ambulatory operations for inguinal hernia (29 operations in ASA group III patients) under unmonitored local anaesthesia [6]. Median postoperative hospital stay was 85 minutes. Two patients needed general anaesthesia, and nine patients (2%) needed overnight admission. One week postoperative morbidity was low with one patient with transient cerebral ischaemia and one with pneumonia, but none with urinary retention. The high satisfaction (88%) on follow-up makes this a triumph for local anaesthesia, but the variation in general practitioners' recommendations for convalescence, such as between one and 12 weeks off work, may need to be changed if the full benefit to the individual and to the society is to be harnessed [7].

### **A complex operation - what is the question? is it still general versus regional?**

Our old question was whether regional or regional supplemented general anaesthesia could produce major reductions in morbidity and mortality - the general versus regional anaesthesia question. An example is vascular surgery. The Yeager study [8] did suggest improvement in patients with regional anaesthesia in patients undergoing abdominal aortic aneurysm or lower extremity vascular surgery. A feature of subsequent studies which showed no difference between regional and general anaesthesia was an increasing extent of control over all aspects of postoperative care [9, 10]. The effect of the detailed protocols was that bad outcomes were reduced in all groups [11]. The implication is that even if there was a difference it

would take a really huge study to show it using the morbidity and mortality outcomes [12]. But the suggestion is that it is only if the postoperative protocols allow any advantage to be expressed, such as advantage in time to feeding or time to walking, that we will see a difference between regional and general anaesthesia. Epidural local anaesthetic may well allow bowel function to return earlier [13], but only if protocol allows it will we see patients going home two days after major surgery [14]. The point is that this radical change is only possible if the procedure is done under an epidural, because the epidural makes it possible for the patient to mobilise early and for bowel function to return earlier.

For some operations there is proven advantage of regional over general anaesthesia. For hip [15] and knee [16] replacements "solid" epidural anaesthesia with sedation during surgery followed by postoperative epidural can produce reduced blood loss, faster surgery, reduced morbidity and faster rehabilitation. In this context change has been gradual rather than radical, but again the key is the epidural, both for the operation and afterwards.

Returning to the old question, general versus regional anaesthesia, a recent set of meta-analyses looked at randomized, controlled trials (RCTs) to assess the effects of seven different interventions on postoperative pulmonary function after a variety of procedures [17]. The seven were epidural opioid, epidural local anaesthetic, epidural opioid with local anaesthetic, thoracic versus lumbar epidural opioid, intercostal nerve block, wound infiltration with local anaesthetic, and intrapleural local anaesthetic. Compared with systemic opioids, epidural opioids decreased the incidence of atelectasis significantly. Epidural local anaesthetics

compared with systemic opioids increased PaO<sub>2</sub> significantly and decreased the incidence of pulmonary infections and pulmonary complications overall. Intercostal nerve blockade did not produce significant improvement in pulmonary outcome measures.

Interestingly on the surrogate measures of pulmonary function (FEV<sub>1</sub>, FVC, and PEF<sub>R</sub>), there were no clinically or statistically significant differences, showing again the importance of choice of outcome measure. The results do confirm that postoperative epidural pain control can significantly decrease the incidence of pulmonary morbidity [17].

### **Where does this take us with local anaesthetics?**

With the local anaesthetics we have now the so-called multimodal approach for the postoperative period, using NSAIDs and paracetamol [1, 18]. Slow release or very long acting local anaesthetics may deliver further radical improvement by improving the postoperative period. Long acting local anaesthetics are not a new thought [19, 20], and the problem is to be sure that the block is indeed reversible and that the extended duration is not due to a toxic effect [21]. The new thought is that instead of focusing exclusively on a particular block or a particular local anaesthetic we need to think of the wider context, and choose our outcomes accordingly. New drug features and new ways of doing particular blocks are obviously important, but should not preclude answering the bigger question.

## **How do we choose which block for a particular procedure?**

An example, albeit a special case, of how to determine the most effective local anaesthetic technique, is the randomized controlled trial of 52 babies which compared ring block, dorsal penile nerve block, a topical eutectic mixture of local anaesthetics (EMLA), and topical placebo for neonatal circumcision [22]. The authors used placebo because it represented current practice, with no anaesthetic for neonatal circumcision. The three treatment groups all had significantly less crying and lower heart rates during and following circumcision compared with the untreated group. The ring block was equally effective through all stages of the circumcision, whereas the dorsal penile nerve block and EMLA were not effective during foreskin separation and incision.

Many of the recent comparisons, for instance in thoracic anaesthesia, of one block against another, are designed as A versus B comparisons. Unless the trials are very big, which most are not, one ends up concluding that the trial showed no difference, and we do not know if the trial was capable of revealing a difference if in fact there was one [23]. Choice of block also involves comparing the morbidity of the contenders. Again size of trial is crucial. Rare events will not be picked up in small trials.

### **Problems with local blocks**

One important question is whether using nerve blocks or powerful epidural techniques has deleterious consequences. For most nerve blocks, for instance axillary brachial plexus block, we just do not know the

incidence of long term nerve problems. In all likelihood it is vanishingly small. In a one- year prospective survey of the French-Language Society of Pediatric Anesthesiologists Giaufre et al reported that 38% of the 24,409 local anaesthetic procedures were peripheral nerve blocks and local anaesthesia techniques. These were reported as "generally safe" [24].

In the same survey "central blocks" (15,013), most of which were caudals, accounted for more than 60% of all local anaesthetic procedures. Their complication rate for central blocks works out at 15 per 10,000 (25 incidents involving 24 patients). These were rated as minor, and did not result in any sequelae or medicolegal action.

In adults a report from Finland [25] reviewed all claims (1987-1993) about severe complications associated with epidural and spinal anaesthesia. Eighty-six claims were associated with spinal and/or epidural anaesthesia. There were 550,000 spinals and 170,000 epidurals. With spinals there were 25 serious complications: cardiac arrests (2), paraplegia (5), permanent cauda equina syndrome (1), peroneal nerve paresis (6), neurological deficits (7), and bacterial infections (4). With epidurals there were nine serious complications: paraparesis (1), permanent cauda equina syndrome (1), peroneal nerve paresis (1), neurological deficit (1), bacterial infections (2), acute toxic reactions related to the anaesthetic solution (2), and overdose of epidural opioid (1). This gives an overall incidence of serious complications of 0.45 per 10,000 for spinal and 0.52 per 10,000 for epidural.

Again in adults a French survey [26] reported on 40,640 spinals and 30,413 epidurals. Of the 98 severe complications 89 were attributed fully or partially to the regional anaesthesia. There were 26 cardiac arrests with spinals ( $6.4 \pm 1.2$  per 10,000 patients), and six were fatal. There were three



arrests with epidurals. Of 34 neurological complications (radiculopathy, cauda equina syndrome, paraplegia), 21 were associated either with paraesthesia during puncture (n = 19) or with pain during injection (n = 2), suggesting nerve trauma or intraneural injection. Neurological sequelae were significantly commoner after spinal anaesthesia ( $6 \pm 1$  per 10,000) than after each of the other types of regional procedures ( $1.6 \pm 0.5$  per 10,000).

Yuen et al [27] described 12 patients (out of an estimated 13,000) with complications after lumbar epidurals. Eleven patients had lumbosacral radiculopathy or polyradiculopathy, ten after epidural and one after subarachnoid injection of medication during intended epidural. One patient had a thoracic myelopathy after an unintended spinal. From their data one may estimate the incidence of short-term (persisting less than one year) neurological sequelae after an epidural as 9 per 10,000, and for longer term (persisting more than one year) 2 per 10,000. As the authors point out these incidences appear to have changed little from previous case series [27].

An important RCT looked at the question of whether there was any difference in long-term cognitive dysfunction after total knee replacement surgery in 262 older adults (median age 69 years; 70% women) after epidural or general anaesthesia [28]. The importance is that it is the largest trial to date of the effects of general versus regional anaesthesia on cerebral function, with more than 99% power to detect a clinically significant difference on any of the neuropsychological tests. Preoperative neuropsychological assessment was repeated postoperatively at 1 week and 6 months. Cognitive outcome was assessed by within-patient change on 10 tests of memory, psychomotor, and language skills. There were no

significant differences between the epidural and general anaesthesia groups on any of the 10 cognitive tests at either 1 week or 6 months. Overall, 5% of patients showed a long-term clinically significant deterioration in cognitive function.

The difficulty in establishing whether a putative risk really is a risk is apparent in the controversy about backache after childbirth epidural.

## **Chronic Pain**

Two aspects of local anaesthetic use in chronic pain, why do blocks last a long time? and the use of epidural corticosteroids for sciatica, are featured because they are of current interest.

### **Why do blocks last a long time?**

Many of us do peripheral nerve blocks with local anaesthetic for pain due to trauma or surgery, and the dogma is that the local anaesthetic block alone can occasionally produce a cure and more often reduce pain for a duration which far outlasts the duration of the local anaesthetic. In a descriptive study Arnér et al reported on thirty-eight consecutive patients with neuralgia after peripheral nerve injury, treated with one or two series of peripheral local anaesthetic blocks [3]. The blocks were technically successful, with all patients experiencing an initial total relief of ongoing pain between 4 and 12 hours. In the 17 patients who had evoked pain (hyperalgesia or allodynia) it was blocked together with the spontaneous pain. In 18 patients the analgesia outlasted the conduction block. Thirteen

patients had complete pain relief for 12 to 48 hours in 13 patients, and in five pain relief was complete for two to six days. Eight patients had a second phase of analgesia, varying from four hours to six days, and coming on within 12 hours of the pain recurring.

Arnér et al chose to concentrate on complete pain relief, and using this yardstick mono- or biphasic prolonged complete analgesia occurred in 25 out of 38 patients. A tantalising further result is that for 15 of the 20 patients who had initial complete analgesia but lasting less than 12 hours partial improvement lasting weeks to months was noted. Conversely only one of the 18 patients who had more than 12 hours initial relief reported prolonged partial improvement. Their paper provides some empirical support for the (common) clinical use of local anaesthetic blocks in this context, also reopens the interesting question of why a block can reduce pain for far longer than the local anaesthetic should work.

Arnér et al discuss systemic uptake and axoplasmic transport of local anaesthetic as putative mechanisms, but their experiments showed little evidence of transport. The explanation may lie in "breaking the cycle". The peripheral pain input is blocked, and system can then reset itself. This begs many questions. For how long does the input have to be blocked to allow the system to reset? For which types of pain is this true? Their study provides clinical legitimacy for further investigation.

## **Epidural corticosteroids for sciatica**

Two systematic reviews have addressed the effectiveness of epidural steroid injections for sciatica and back pain. Both examined the randomised controlled trials published up to the end of 1994.

The analysis by Koes and colleagues from Amsterdam [29] goes into great depth examining methodological quality of the trials and how this has been scored by the reviewers. This type of review is, frankly, disappointing and does not produce any meta-analytic judgements on which to work, and few enlightening ideas about the future research agenda other than some anodyne comments about possible trial design.

The best that this review can do is to tell us that, of the four studies with the highest methodological quality assessed by their particular scoring system, two had positive outcomes for epidural steroids (judged by their authors) and two had negative outcomes.

In contrast, a meta-analysis of the same trials by Watts and Silagy [30] is an important step forward in showing that epidural corticosteroids have an analgesic effect on sciatica compared with control. Their analysis, using odds ratios, answered the question "Do epidural steroids work?".

We wished to address the question "How well do they work?", to try to assess the extent of the benefit given by the steroids. To do this we re-analysed their data, and adding a new trial (Carette et al [31]) used NNT [32] as the measure of clinical benefit (Table 1), using the outcome of at least 75% pain relief for short-term outcomes (1 - 60 days) and at least 50% pain relief for long-term outcomes (12 weeks to one year). In circumstances where the numbers of patients entered into individual studies is small, this approach is most likely to produce a reliable indication of the clinically relevant outcomes needed by patients, providers and purchasers in making decisions about a technique which carries small but finite risk (see above).

## **Table 1: Epidural corticosteroids for sciatica**

### **Short-term relief**

There were eleven trials which gave short-term relief data (more than 75% pain relief), with 319 patients given epidural steroids, and 345 given placebo. Only three of these studies were themselves statistically significant [35, 41, 42], but overall there was a statistically significant benefit (1.5 with 95% confidence intervals 1.2 to 1.9).

The NNT for short-term (1 to 60 days) greater than 75% pain relief from the ten trials with short-term outcomes combined, was just under 7.3, with 95% confidence intervals from 4.7 to 16. This means that for 7 patients treated with epidural steroid one will obtain more than 75% pain relief short-term who would not have done had they received the control treatment (placebo or local anaesthetic).

### **Long-term relief**

There were six trials which gave long-term relief data with 315 patients given epidural steroids, and 395 given placebo. Only one of these studies was itself statistically significant [37], but overall there was a statistically significant benefit (1.3 with 95% confidence intervals 1.1 to 1.5).

The NNT for long-term (12 weeks up to 1 year) improvement from the six trials combined, was about 13 for 50% pain relief, with 95% confidence intervals from 6.6 to 314. This means that for 13 patients treated with epidural steroid one will obtain more pain relief over this longer term

period who would not have done had they received the control treatment (placebo or local anaesthetic).

## **Conclusion**

These NNT values at first sight appear disappointing. Here is an intervention which shows statistically significant improvement compared with control, and yet the clinical benefit, the number-needed-to-treat for one patient to reach the chosen end-point, is 7 for short-term benefit and 13 for long-term. The short-term end-point, however, is quite a high hurdle. Using an easier hurdle of 50% relief rather than 75%, the 'best' NNT achieved by drug treatment of neuropathic pain was just under 3. Patients may choose the epidural if it means they do not have to take medication, particularly if it gives a higher level of relief, even though there is a 1 in 7 chance of this level of response.

The long-term NNT of 13 is perhaps not surprising. Occasional patients in most clinics report a 'cure' as a result of a steroid epidural, but the majority of epidural steroid successes return for repeat epidurals. That one patient has relief lasting between 12 weeks and a year for twelve treated with epidural steroid fits with experience.

The message is that we will have inevitably to expose our practice to the searching type of analysis which Watts and Silagy have used for epidural steroid. This intervention has shown a statistically significant benefit over control. Others will not, and will be discarded. For those interventions which do show statistically significant benefit over control there is then a further stage, which is to define the clinical benefit of the intervention. The NNTs for effectiveness are one possible definition, particularly when

coupled with NNTs for minor and major harm (NNT of about 40 for dural tap in [30]).

For patients with chronic disease, and in this case chronic painful disease, interventions may be attractive even if their success rate is far lower than would be acceptable in, say, the management of postoperative pain. This means that the interpretation of measures of clinical benefit, such as NNTs, has to be context-dependent. For the moment we need the best possible analysis, as Watts and Silagy have demonstrated, of the data available. If the data is poor then that establishes the clinical research agenda. If the data is reasonable then we can try to define measures of clinical benefit. The art of clinical practice will then come into play, as patient and doctor juggle the risk and benefit of the alternatives, albeit with better data than we have at present.

## **More on epidurals - local anaesthetic and opioid**

For over twenty years we have known that opioids applied to the spinal cord have analgesic effect. It has proved surprisingly difficult to define a clinical role for spinal (epidural and intrathecal) opioids, maximising the analgesic benefit while minimising the risk. The original question addressed was the advantage of spinal opioids over spinal local anaesthetics. The next question was the advantage of spinal opioids over intramuscular, oral or subcutaneous opioids. Now we have come full circle because it is the use of spinal combinations of local anaesthetic and opioid which promises the greatest clinical benefit.

It is ironic that these questions are being addressed for spinal opioids while our ignorance about the conventional routes of administration for opioids, whether oral, subcutaneous, intramuscular or intravenous, remains profound. The single most important point is to distinguish between the phenomenon, "it can be done", and the clinical questions, "should it be done?", and if so when and to whom? New routes often have a high profile so that it may be very difficult to determine their real clinical role. The ultimate arbiter of the clinical role is the risk:benefit ratio. The aim is better analgesia with fewer adverse-effects and with no increase in morbidity. For instance in chronic pain oral opioids can provide good relief with manageable adverse effects for the majority of patients. New routes must be considered as replacements, adjuncts or alternatives to the oral route.

Well-designed randomised controlled trials which compared the new route with the established routes would give us the answers. There are still few such trials available. They are hard to do well, particularly in chronic and cancer pain.

The underlying issues for new routes are kinetic and clinical logic. The spinal routes have the kinetic logic of applying the opioid directly to opioid receptors in the cord. The clinical advantage sought is better analgesia without the problems of systemic opioid use, or even the same analgesia with fewer adverse effects. Proposed alternatives must provide an improved risk:benefit ratio and be logistically feasible.

## **Underlying issues**



## **The Epidural Space**

The spinal epidural space extends from the sacral hiatus to the base of the skull. Drugs injected into the epidural space can then block or modulate afferent impulses and cord processing of those impulses. The way in which they block and modulate impulses and processing is probably the same as the mechanism which operates when the same drugs are injected intrathecally. There are some important differences between the epidural and intrathecal spaces, however, which affect clinical practice. It is the fact that the epidural space is a relatively indirect method of access compared with intrathecal that provides potential clinical advantage compared with the intrathecal route, but also complicates matters.

The epidural space provides access for drugs to the neuraxis, as does intrathecal injection. The potential clinical advantage of an epidural is the fact that the meninges are not physically breached, so that headache from cerebrospinal fluid (CSF) leakage does not occur, and the danger of meningitis is also reduced. Chronic administration through catheters should therefore be safer by the epidural route than by the subarachnoid route. The first disadvantage is that the epidural space is vascular and contains fat. A large proportion of the epidural dose is taken up by extradural fat and by vascular absorption and so less drug is immediately available for neural blocking action. The second disadvantage is that the epidural tissues react to foreign bodies more than the sheltered subarachnoid space. Epidural catheters often become walled off by fibrous tissue within days to weeks, whereas intrathecal catheters are much less prone to blockage [44]; this problem is in part overcome by using continuous infusion rather than intermittent bolus.

## **Reaching the Site of Action**

It used to be thought that the dura mater was impermeable to local anaesthetics and that epidural block with local anaesthetic occurred at the mixed nerve and dorsal root ganglia beyond the dural sleeves surrounding each pair of anterior and posterior spinal roots. Radioactive tracer studies have shown that the dura mater is not impermeable, and that subarachnoid and epidural local anaesthetics act at precisely the same sites, namely the spinal roots, mixed spinal nerves and the surface of the spinal cord to a depth of 1 mm or more, depending on the lipid solubility of the anaesthetic [45]. With both epidural and subarachnoid injection the local anaesthetic drug entered the CSF and remained there until taken up by the lipids of the cord and spinal roots, or until 'washed out' by vascular uptake into the blood vessels of the region.

### **Figure 1: Diagram of epidural space and fate of injected drugs, which may go into fat, into blood or into CSF and then into the spinal cord**

Opioids have to reach the opioid receptors in the substantia gelatinosa of the cord in order to have spinal effect. Some of the opioid injected into the epidural space will reach the CSF and then the cord. Some will be absorbed into the blood stream, and some will be bound by fatty tissue in the epidural space. The proportion of the dose injected which goes in each of these directions depends on lipid solubility and on molecular weight [46]. Lipid soluble opioids will be subject to greater vascular uptake from the epidural space than lipid insoluble opioids. High molecular weight drugs diffuse across the dura with less ease than drugs of low molecular weight. Once across the dura drugs which have low lipid solubility may maintain

high concentrations in the CSF for long periods of time, and so can spread rostrally. Sampling at cisternal level after lumbar intrathecal injection of morphine confirmed that high concentrations are found within an hour [47]. Drugs with high lipid solubility will be bound much faster in the cord, leaving lower concentrations of drug in the CSF available to spread rostrally.

There is a similar range of lipophilicity and molecular size for the two drug classes, local anaesthetics and opioids, so that the journey from the place of injection to the target sites is likely to be accomplished in roughly the same time span for both classes of drug, and proportional losses by vascular absorption and uptake into neighbouring fat depots are also likely to be similar. With both local anaesthetics [48] and opioids [49], vascular uptake is slowed and neural blockade increased by adding a dilute concentration of adrenaline (3-5 µg/ml) to the injected agent.

### **Lipophilicity and Potency**

Within each class of drug, however, there is a wide range of lipophilicity, and this may have considerable influence on the relative potencies of the drugs within a class. Using an electrophysiological model, single unit recordings were made in the lumbar dorsal horn in the intact anaesthetised rat from convergent, multireceptive neurones. Activity was evoked by A $\beta$  and C fibre transcutaneous electrical stimulation of hindpaw receptive fields. With intrathecal application of opioids the effect of lipid solubility in determining relative intrathecal potency was measured. Initially four  $\mu$  opioid receptor agonists were used, morphine, pethidine, methadone and normorphine, because all four drugs had relatively high affinity for  $\mu$  and little for  $\delta$  and  $\kappa$ , precluding receptor affinity to other

receptor subtypes as a complicating factor. The ED<sub>50</sub> values from the dose-response curves were expressed against the partition coefficients. A significant correlation was found between the log ED<sub>50</sub> and lipophilicity, but this was an inverse relationship, so that the least lipid soluble agonists, morphine and normorphine, were the most potent, and the highly lipid soluble methadone was considerably the least potent.

The same approximate order of potency, morphine = normorphine > pethidine > methadone, was seen in behavioural hot plate and tail flick tests, although the cut-off maxima necessary in those tests made it difficult to determine an ED<sub>50</sub> for the more lipophilic and hence less potent compounds [50]. In a second study [51] three opioids, fentanyl, etorphine and buprenorphine, all highly potent by the systemic route in man and animals, were applied either intrathecally or intravenously. Figure 2 shows the relationship between intrathecal potency and lipophilicity for the 7 opioids tested. For fentanyl and buprenorphine potency correlated well with lipophilicity. The potency of etorphine, however, was considerably greater than would be expected if lipophilicity was the only determinant.

### **Figure 2: Relationship between lipophilicity and potency**

Non-specific binding is the probable explanation of the inverse correlation between intrathecal potency and lipid solubility. When radiolabelled opioid distribution was visualised by autoradiography [52] the highly lipid soluble opioids were found to be restricted largely to fibre tracts, and penetrated the grey matter poorly. The thickly myelinated large A fibres cap the spinal cord grey matter. They pass medially over the dorsal horn before penetrating the grey matter. This means that the lipid rich A fibres

come between the injection site and the opioid receptors in the grey matter. Lipid soluble opioids will be taken up rapidly but preferentially in this lipid rich tissue. Drug bound in this non-specific way cannot then go on to bind to the receptors.

Systemic potency ratios in man are thus unlikely to be accurate guides to spinal effectiveness, which makes it difficult to choose the dose of intrathecal (or extradural) opioid necessary to produce the same analgesia as a given dose of morphine. Many of the epidural opioid studies which used opioids other than morphine have used the systemic potency ratio to morphine as the guide for spinal potency. Extrapolation from the animal data suggests that for drugs with high lipophilicity the intrathecal dose required to give analgesia equivalent to that produced by a 0.5 mg bolus dose of intrathecal morphine is likely to be of the order of 5 mg for pethidine and close to 8.5 mg for methadone.

Clinical studies support this argument. Systemically, methadone is equipotent to morphine. From the animal work intrathecal methadone was approximately 18 fold less potent than intrathecal morphine [53]. An intrathecal dose of 0.5 mg of morphine provided significantly superior analgesia to 20 mg of methadone [54].

For extradural use life is even less straightforward. Previous calculations showed that the proportion of an extradural dose transferred across the dura could vary from up to 20% for morphine (low lipid solubility) to 0.2% for buprenorphine (high lipid solubility) [46]. Because of the significant inverse correlation between lipid solubility and potency shown for the drug once in the cerebrospinal fluid, the extradural dose of highly lipid

soluble drugs may have to be surprisingly high to give effect equianalgesic to that of 5 mg of extradural morphine.

The clinical results around this theory remain conflicting. No clinical advantage was seen with extradural fentanyl compared with intravenous injection of the same dose, either in postoperative orthopaedic pain [55] or after caesarean section [56]. After laparotomy intravenous alfentanil (0.36 mg/h), combined with epidural bupivacaine 0.125%, was as effective as epidural alfentanil (0.36 mg/h) [57]. The classic danger of course is that these are A versus B trial designs often with small numbers of patients. The trials may be insensitive to real differences. Others have found epidural fentanyl to provide superior analgesia compared with intravenous fentanyl, after thoracotomy [58], during childbirth [59] and after Caesarean section [60]. These trials are also small, with maximum group size of 20. The trials in childbirth and after Caesarean section really investigated epidural fentanyl plus local anaesthetic rather than fentanyl alone. We would conclude that this controversy shows the necessity of systemic controls in extradural studies, because the vascular uptake of a lipophilic drug from the epidural space will in itself result in analgesia and is similar in its time course and extent to the uptake seen after the same dose given parenterally.

We would also contend that lipophilic opioids on their own (not combined with local anaesthetic) are a poor choice for epidural use; non-specific binding means that they have low spinal potency, and substantial systemic analgesic effect makes it difficult to determine any spinal action. In practice bolus injection of epidural opioid often is given with, or soon after, injection of epidural local anaesthetic. Clinical impressions of good analgesia after epidural injection of lipophilic opioid may reflect

synergism between the opioid and the local anaesthetic and systemic effect of the opioid.

### **Combinations of Local Anaesthetic and Opioid**

Epidural opioids on their own did not provide reliable analgesia in several pain contexts [61, 62]. Empirically combinations of local anaesthetic and opioid were found to work well, and extradural infusions of these combinations are used widely now for postoperative pain. The benefit is analgesia with minimal motor block and hypotension.

Two experimental studies have confirmed synergism between local anaesthetic and opioid (Figure 3). Using visceral as well as conventional behavioural tests Maves and Gebhart did an isobolographic analysis for morphine and lignocaine [63]. They showed that the analgesic effect of the intrathecal combination was greater than would be expected for a simply additive relationship. Using an electrophysiological model Fraser et al compared the dose-response curve for lignocaine combined with a dose of morphine with the dose-response curve for lignocaine alone. Adding morphine, at a dose well below the ED<sub>50</sub>, produced a 10-fold leftward shift in the lignocaine dose-response curve [64].

These studies support what has been observed clinically, that doses of local anaesthetic and opioid, doses which might be regarded as homeopathic for either drug independently, can produce good analgesia. Neither study was designed to answer the important question of the minimal effective doses of the combination components. While the minimum effective doses will vary with pain context, studies answering the question for one type of pain may tell us which component is the prime mover. The mechanism of the

synergy is not known. It may be that the local anaesthetic, by reducing the afferent input, is moving the opioid dose-response to the right. Such explanations, however, only account for one direction of synergy, and the evidence suggests that the synergy is bi-directional (Figure 3). Clinical observations suggest that chronic infusion of the combination can produce selective blockade, blocking pain fibres while leaving other sensory input (and motor function) intact. These contradict the observation that block of pain by epidural opioid alone is associated with blunting of sensitivity to cold and pin-scratch sufficient for a segmental effect on cutaneous sensation to be detectable [65]. Such selectivity may of course be dose-dependent.

## **Other Drugs**

Many drugs have been given as analgesics via the epidural route. Steroids given for the management of back pain have already been mentioned. Caveats about toxicity are necessary.

### Alpha-2 Adrenergic Agonists

In both electrophysiological [66] and behavioural studies alpha-2 adrenergic agonists have antinociceptive effect. Much of the early work was with clonidine, and this may have been misleading in terms of the properties of purer alpha-2 adrenergic agonists. Intrathecal clonidine showed a plateau at 50% of maximum effect. The newer drug, dexmedetomidine, is considerably more potent than clonidine and did not show such a ceiling to antinociception [67].



Alpha-2 adrenergic agonists have synergistic effect with both spinal opioid [66, 68, 69] and spinal local anaesthetic (Figure 3). The evidence for the local anaesthetic interaction comes mainly from clinical studies [70-74].

**Figure 3: Diagram of interactions between epidural local anaesthetic, opioid and alpha-2 adrenergic agonists**

Midazolam

Midazolam on its own has very limited antinociceptive effect in standard behavioural or electrophysiological models [75, 76], although effects have been found in other models [77, 78]. Midazolam may have effects on A $\delta$  fibres [75], and may interact when combined with opioid [79].

**Therapeutic aspects**

Both epidural local anaesthetics and epidural opioids can produce analgesia. The adverse effects of the two drug classes are different. Epidural local anaesthetics can produce hypotension because of sympathetic blockade, and carry the risks of local anaesthetic toxicity for which there is no specific antagonist. Epidural local anaesthetics produce motor block in a dose-dependent way. Epidural opioids can produce delayed respiratory depression, urinary retention, pruritus and nausea and vomiting, particularly in the opioid naive patient. Naloxone is a specific antagonist. Epidural opioids do not produce a motor block. The combination of epidural local anaesthetic and opioid can also produce pain relief, and the synergism between the drug classes offers the potential of effective analgesia at low doses of the components, minimising the adverse effects of both. These features are summarised in Table 2.

**Table 2: Effects of local epidural anaesthetics, epidural opioids and of the combination**

Analgesic effect of epidural analgesics can be measured by a number of techniques, directly by measuring decrease in intensity or increase in pain relief, or indirectly via decreased need for other (parenteral) analgesics. Comparison with other, non-epidural, methods of pain relief has also involved indirect measures, such as the relative effects on respiration, time for patients to recover and effects on stress hormones. The ultimate arbiter has to be analgesic effect, because indirect measures, such as reduction of the expected rise of stress hormones, do not have a direct relationship with analgesia.

For many years randomised controlled trials which compared the analgesia and adverse effects of oral or parenteral analgesics used the rule that sensible comparisons of adverse effect incidence can only be made when the study drugs are compared at equi-analgesic dosage. Very few randomised controlled trials which compare the adverse effects of different epidural opioids (or indeed epidural opioids with other techniques) have made equianalgesia the key criterion. Pronouncements about relative incidence of adverse effects can carry little weight unless the disparity in incidence or severity is measured at doses which produce equivalent analgesic effect.

The clinical decision to use epidural analgesia for pain relief is just that, a clinical decision. It presupposes that the analgesia is as good or better than analgesia from lower technology methods, that the potentially higher risk of adverse effects is worthwhile, and that the facilities exist to deliver the

epidural analgesia effectively and safely. Combination techniques are superseding the use of epidural opioids on their own, and the randomised controlled trials to define the clinical role are still emerging.

## **Acute pain**

### Analgesia

Although both epidural local anaesthetics and epidural opioids can produce analgesia there is some doubt about the ability of epidural opioids to produce as good analgesia [61] as epidural local anaesthetics in severe pain states. In childbirth the degree of analgesia was inadequate to relieve the pain of second stage labour [61, 80], although satisfactory relief of first stage pain could be achieved. No such doubt is seen with the epidural combination of local anaesthetics and opioids. The difference between the pain severity of different pain states should be emphasised, because it also means that categoric prescriptions for the doses to be used in combination infusions are likely to be valid only for a particular pain state or set of circumstances. Indeed the dynamic nature of postoperative pain means that the dosage required on the day of surgery may be much higher than the dosage required on subsequent days.

A clear demonstration of the advantage of the combination of local anaesthetic and opioid was seen in a comparison of 0.125% bupivacaine in saline, diamorphine 0.5 mg in 15 ml and diamorphine mixed with 0.125% bupivacaine (0.5 mg in 15 ml) infused at a rate of 15 ml/h for pain after major gynaecological surgery. The combination produced significantly superior analgesia to either of its components alone, without major adverse effects [81]. Giving the diamorphine intravenously with epidural

bupivacaine was significantly less effective than giving the same dose epidurally in combination with epidural bupivacaine [82].

Many important questions are still to be answered. One practical issue is the ability of combination infusions to control pain remote from the catheter site, as with thoracic pain and a lumbar catheter. Another is whether there is any difference in efficacy or adverse effects if the drugs are given continuously rather than intermittently. For local anaesthetic alone there was little difference [83].

### *Combination Dosage*

Three strategies in dosage are discernible, the low [81, 84, 85], the intermediate [86, 87], and the high [88-90]. High doses (bupivacaine 0.5% 25 mg/h and morphine 0.5 mg/h) were used to produce analgesia immediately after upper abdominal surgery but at some risk [90]. The stress response was not blocked. Lower doses (bupivacaine 0.1% 4 mg/h and morphine 0.4 mg/h) did not provide total pain relief after thoracotomy [85]. The issue of the minimum effective dose is of great importance, and unfortunately may have to be defined for particular circumstances. It is too early (and too circumstance-dependent) for consensus to emerge, but an intermediate dose, 0.25% bupivacaine 10 mg/h with morphine 0.2 mg/h, has its advocates for use in pain after major surgery.

## *Other Analgesics*

### *Alpha-2 Adrenergic Agonists*

The rôle of these drugs as analgesics on their own remains unclear. It is very difficult to preserve the double-blinding in studies of alpha-2 adrenergic agonists because of the hypotensive and sedative effects of the drugs. Comparisons of epidural clonidine with epidural placebo for postoperative pain relief are all marred by this fault because significant hypotension was a feature [91-93]. No analgesic dose-response curve could be defined for clonidine [94].

There is clear evidence, however, for both enhancement of the effect of local anaesthetics [70-74] and enhancement of the effect of opioids. With fentanyl [95] and sufentanil [96] duration of effect was extended; with morphine Motsch et al [97] found that adding clonidine produced significantly better pain scores. There may thus be an adjuvant rôle for alpha-2 adrenergic agonists.

### *Midazolam*

Midazolam is reported to have analgesic effect in postoperative pain (see [98]) but this is hard to understand in view of the drug's failure in animal nociceptive pain models.

## ADVERSE EFFECTS

### *Toxicity*

Epidural delivery necessarily places drugs at the neuraxis. Toxicity is therefore a real risk. Standard epidural analgesics, specifically local anaesthetics and opioids, have not produced toxicity to date, and clonidine was tested before it was used. Perhaps the major worry is if new analgesics without toxicology are introduced.

### *Motor Block*

Techniques of epidural local anaesthesia have been refined to a point where the neural pathways conducting pain can be blocked with a high degree of anatomical selectivity, but motor block is an inevitable accompaniment if large doses of local anaesthetic are needed to stop the pain. In labour pain the motor block results in a higher incidence of instrumental delivery compared with non-epidural pain relief [99] and perhaps in a higher incidence of Caesarean section [100]. This motor block is not seen with epidural opioids alone or when low doses of local anaesthetic are combined with opioid.

### *Vasodilatation & Hypotension*

Vasodilatation in the lower parts of the body from blockade of sympathetic vasomotor nerves in the segments involved is another inevitable accompaniment of epidural local anaesthetic. In labour this requires prophylaxis. Hypotension also occurs with alpha-2 adrenergic agonists, and their use in combination with local anaesthetics could accentuate the risk.

Again the risk is minimised with epidural opioids alone or with the low doses of local anaesthetic used when combined with opioid.

### *Respiratory depression*

Epidural block with local anaesthetics of intercostal and abdominal muscles is unlikely to cause significant impairment of respiratory function unless the phrenic segments (C3, C4 and C5) are also blocked. Respiratory depression after epidural opioids in opioid-naive subjects is much more subtle, more delayed in onset and longer lasting. The epidural opioids all reach the CSF by diffusion through the meninges, and variable degrees of cephalad spread occur within the CSF. Morphine, being relatively less lipid-soluble, will maintain substantial CSF concentrations to a greater extent than more lipid-soluble drugs, increasing the chance of drug reaching opioid receptors in the brain and so increasing the chance of respiratory depression. In volunteers 10 mg of epidural morphine produced a depression of the CO<sub>2</sub>-response curve far greater than that seen after intravenous administration, with the nadir of depression between the sixth and 12th hours after administration [101].

Profound respiratory depression may be precipitated if other opioids are given parenterally during this danger period. Precautions must be taken to see that this mixed type of medication is avoided, and that patients are under appropriate surveillance, so that any case of delayed respiratory depression can be treated promptly [102]. Life-threatening apnoeic intervals can also arise abruptly after small doses of epidural opioids alone, with little warning. Theoretically highly lipid-soluble opioids such as fentanyl and sufentanil should be less prone to rostral spread in the CSF. In practice volunteer studies suggest that although apnoeic intervals after epidural

sufentanil were less frequent and less prolonged than after morphine [103], at equianalgesic doses of the drugs the CO<sub>2</sub>-response curve was depressed and displaced equally severely.

Epidural opioids given on their own for relief of acute pain in opioid-naive subjects are only as safe as the quality of surveillance that is given. Whether the lower doses used in combination with local anaesthetics reduce the risk has still to be established.

### *Systemic Effects*

With epidural opioids systemic effects of the opioid are to be expected. Vascular uptake from the epidural space is appreciable, with blood concentration curves of opioid which are almost indistinguishable from those after intramuscular or intravenous administration (see for morphine [65, 104, 105]). All the adverse effects of systemic opioids should therefore be expected. Placental transfer of opioid to the foetus and subsequent neonatal respiratory depression are thus not prevented by changing from parenteral opioid to epidural opioid.

### *Bladder function*

Urinary retention is a common complication of epidural analgesic techniques after either local anaesthetics or opioids. The incidence appears to be dose-related, and in the case of local anaesthetics retention is probably due to bladder deafferentation because the distended bladder does not give rise to discomfort. With epidural opioids the mechanism seems to be more complicated, because retention and bladder distension to volumes



above 800 ml in volunteers gave rise to marked discomfort and distress [106].

Urodynamic and electromyographic studies in male volunteers indicated that the cause was detrusor muscle relaxation and not increased motor activity in the pelvic floor muscles [107]. The origin of this detrusor relaxation is unclear, but the time sequence mirrors that of antinociception, beginning within 15 minutes but taking about 60 minutes to reach peak effect, and then lasting 14-16 hours. The overall intensity and duration of bladder relaxation appears to be independent of dose within the range of 2-10 mg. Retention with epidural opioids, like all the other adverse effects of epidural opioids, can be relieved by naloxone, although repeated doses may be needed to ensure complete evacuation of the bladder [106].

The high incidence of retention from either local anaesthetic or opioid blockade is a factor in the clinical decision to use epidural analgesia.

### *Pruritus*

Pruritus is not seen after epidural local anaesthetics, but it is a frequent adverse effect of epidural opioids in the opioid naive patient. The itching is usually generalised but can be in the analgesic segments. The cause of the pruritus is unclear. The onset is often hours after analgesic effect is established, perhaps suggesting modulation of cutaneous sensation in the cord. Pruritus can be a major problem in acute pain management with epidural opioids, severe enough to cause distress. It can be reversed by naloxone, but then the analgesia is likely to be reversed.

### *Long-term Risks*

Argument continues about whether or not epidural local anaesthetics in childbirth can cause chronic backache [108, 109]. We still need a true RCT to clarify the issue; difficult labours are more likely to need epidural block and may be associated with a higher risk of backache. If it is indeed motor block with local anaesthetic which is the cause, rather than the delivery or the epidural procedure per se, then the use of opioids or combinations should be preferred.

### **Chronic pain**

Epidural analgesics have roles in both chronic non-malignant pain and cancer pain.

#### Chronic Non-malignant Pain

In chronic non-malignant pain the primary role for epidural local anaesthetics is their injection combined with steroid for the management of back pain with the object of reducing local oedema and nerve-root compression, although block of C fibre transmission [110] may be the mechanism of the analgesia claimed. The trials have been mentioned above.

Epidural opioids alone have little place in the long-term management of on-going non-malignant pain (but see [111]), although acute exacerbations may be handled on a one-off basis.

The rôle of epidural clonidine is contentious. Apart from its ability to extend the duration of local anaesthetics it may have the ability to relieve some forms of neuropathic or deafferentation pain. Glynn et al [112] found epidural clonidine to be as effective as epidural morphine in 20 chronic pain patients using a crossover design. As in earlier studies there was a suggestion that clonidine was more effective than morphine for neuropathic pain, and it may be that alpha-2 adrenergic drugs find a place as adjuvants in local anaesthetic and opioid combinations for resistant neuropathic pain. This suggestion is supported by the findings in neuropathic cancer pain [113].

Epidural midazolam was found in one randomised controlled trial to be as effective as epidural steroid in the management of chronic back pain [98]. Experience is limited, so that more studies are needed to clarify if there is a clinical rôle.

### Cancer Pain

Epidural opioids are used in chronic cancer pain as an alternative to other (oral or subcutaneous) routes [111]. There has been little evidence from randomised controlled trials to support the argument that better analgesia is provided at lower incidence of adverse effects. Indeed one trial found that subcutaneous opioid was just as good as epidural opioid alone [114].

Long-term administration, either as intermittent bolus or by infusion, is technically feasible. The choice of delivery system lies between the low technology percutaneous exterior epidural catheter and micropore filter, tunnelled subcutaneous catheter with external injection port and micropore filter, to high technology totally implanted system with small

subcutaneous reservoir and injection port, totally implanted system with large internal reservoir and automatic metered or manually controlled dosing device. Implanted systems are more likely to maintain hygiene and convenience, in theory protecting from infection and mechanical displacement. Implanted devices have high initial costs compared with simple percutaneous approaches, but over a period of months this may even out because of the higher costs of maintaining or replacing percutaneous catheters.

These technical approaches for administering small metered doses of spinal morphine over periods of weeks or months have proved to be well suited to home management, and highly appreciated by the patients and their families. The problems include blockage, infection, pain on injection and leaks [111]. It is important to be sure that the patient's pain cannot be controlled by simpler routes and that it can indeed be controlled by this method before embarking on what is a substantial undertaking [115]. Preliminary trials with a percutaneous catheter to assess the effectiveness and the acceptability of adverse effects are necessary.

The main argument against the use of the epidural route as (merely) an alternative way deliver opioid is that the opioid, whether given orally or spinally, must in the end be working at the opioid receptor. Failed management with oral opioid, failed because the pain was not responsive [116, 117] rather than failed because the opioid was not absorbed, is thus a questionable indication for epidural opioid. The protagonists can point to many thousands of patients treated. Epidural opioids alone, however, are not a universal panacea in cancer pain [62]; if conventional routes for opioids do not relieve the pain, combinations of local anaesthetic and opioid appear to have a higher success rate than opioid alone.

A systematic review [118] compared the efficacy of epidural, subarachnoid, and intracerebroventricular opioids in cancer. Intracerebroventricular therapy appeared at least as effective against pain as other approaches, and was the only fixed system associated with fewer technical problems than the use of simple percutaneous epidural catheters.

#### *Combination of Local Anaesthetic and Opioid*

The situation is changing with the advent of epidural infusion of combination of local anaesthetics and opioid. Intrathecal use of such combinations in cancer pain is described by Sjöberg et al [119]. Most cancer pain, some 80%, responds to simple management with oral opioid and other analgesics. The two kinds of pain which respond badly to simple management are movement-related pain and neuropathic pain.

Movement-related pain can theoretically be controlled with oral opioid. In practice the dose of opioid required to control the patient's pain on movement is such that the patient is soundly sedated when not moving (not in pain). Conventional wisdom is that NSAIDs should be added if they have been omitted. In practice this often has little impact. Some such pains, for instance due to vertebral metastases, can be helped by extradural steroid. The final resort is to use continuous epidural infusion of a combination of local anaesthetic and opioid. The synergy between the local anaesthetic and the opioid means that low doses can provide analgesia with little loss of mobility. There are few randomised controlled trials of this usage. The need for greater volume means that few of the devices available for implanted infusion of opioid alone are suitable, so that percutaneous catheters and external syringe drivers may be necessary. This

method appears to produce analgesia for pains poorly responsive to opioids alone. The logic then is that pains poorly responsive to opioid orally are unlikely to improve simply by changing the route by which the opioid is given. Epidural use of local anaesthetic and opioid can produce the necessary analgesia.

The management of neuropathic cancer pain is often not straightforward. If such pain cannot be controlled by opioid, antidepressant or anticonvulsant, and steroids are inappropriate, then again epidural infusion of a combination of local anaesthetic and opioid should be considered. An RCT of 85 patients comparing 30 µg per hour epidural clonidine with placebo for 14 days showed successful analgesia was commoner with epidural clonidine (45%) than with placebo (21%), and more so in neuropathic pain (56% vs. 5%) [113]

## **Conclusion**

Epidural local anaesthetics have been used for many years in the management of acute pain in trauma, surgery and obstetrics, as well as in chronic pain, and their limitations and capabilities are well-understood in these clinical areas. Opioids by this route are a new departure, and our short experience in human subjects dates from as recently as 1979. Early enthusiasm in this field has been tempered by randomised controlled trials, and the field remains dynamic, with a switch from the use of either local anaesthetics or opioids on their own to the combination of the two. The alpha-2 adrenergic agonists in existing forms may also have a limited role on their own but may interact with local anaesthetics and opioids to provide a clinical advantage. Their importance is that they suggest that other beneficial interactions may emerge.

The fact that the field is dynamic, with a recent switch to the combination of local anaesthetics and opioids, means that we do not yet have the necessary information as to minimal effective dose. Randomised controlled trials are then required to define the clinical role of epidural combinations versus non-epidural pain relief in all the various pain contexts. There is still major concern that these powerful analgesic tools should be used effectively, safely, and economically. The dream of attaining prolonged and powerful analgesia without adverse effects has not yet been realised, and as far as these epidural techniques are concerned, pain relief must still be bought at the cost of some risk. In some areas of pain management, however, these techniques are changing radically the quality of the service we deliver.

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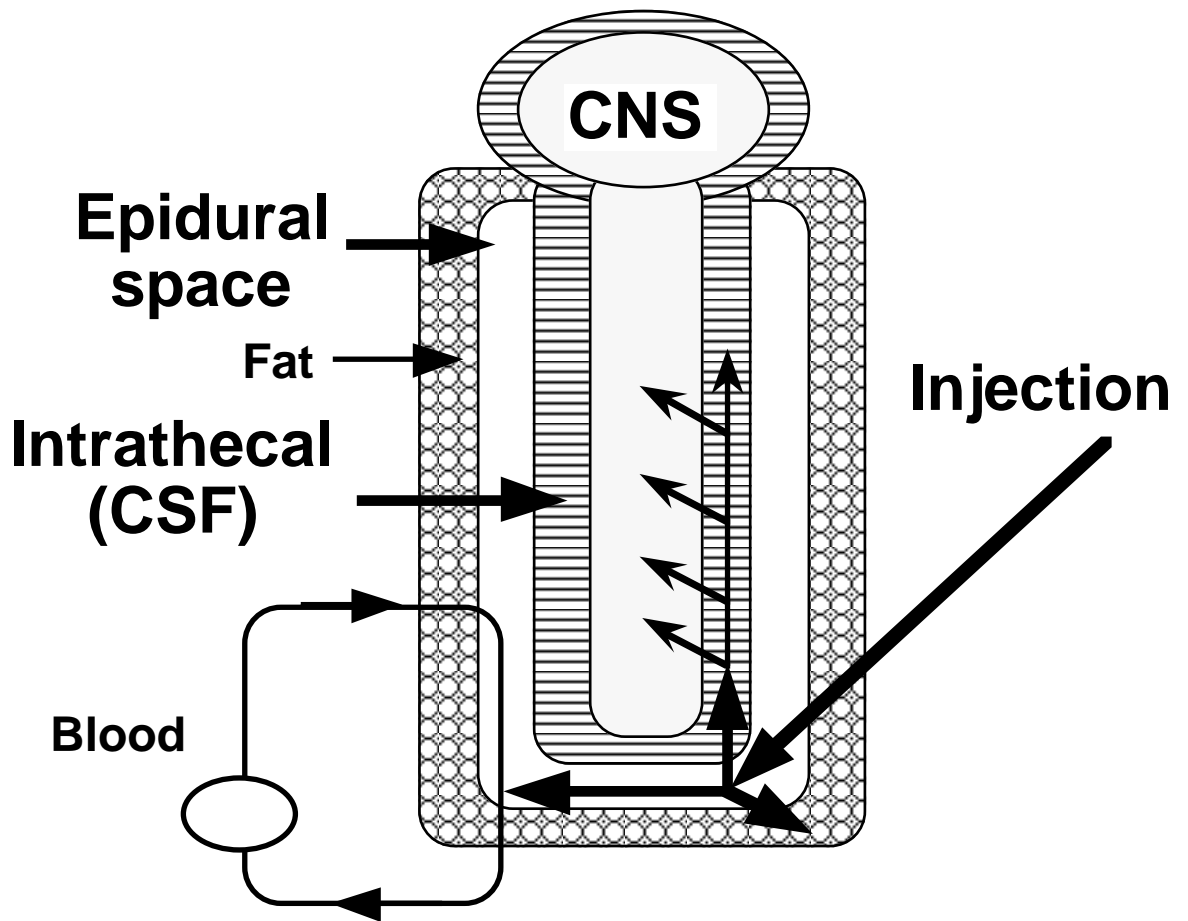
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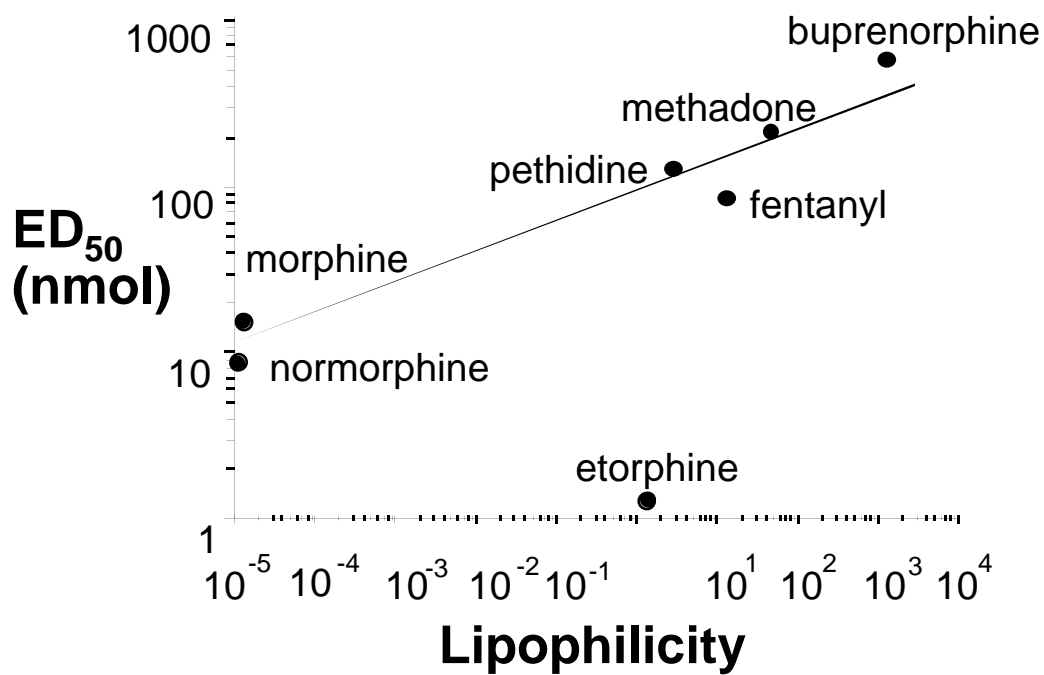
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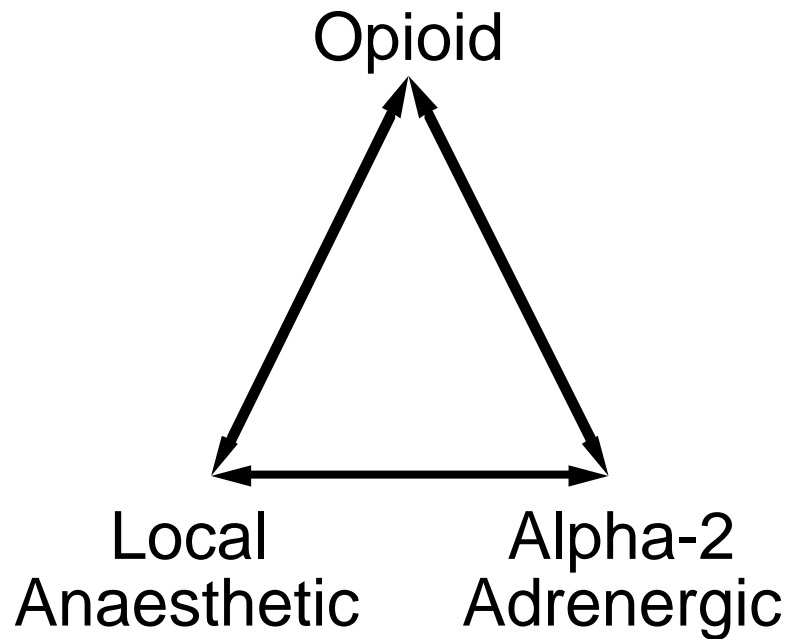
**Figure 1** Diagram of epidural space and fate of injected drugs, which may go into fat, into blood or into CSF and then into the spinal cord.



**Figure 2** Redrawn from [51]. The relationship between lipophilicity (heptane/water partition coefficient) and potency ( $ED_{50}$  nmol) for morphine, normorphine, pethidine, methadone buprenorphine, etorphine and fentanyl.



**Figure 3** Diagram of interactions between epidural local anaesthetic, opioid and alpha-2 adrenergic agonists. The relationships with midazolam are not clear.





Epidural and spinal anaesthetics. An epidural anaesthetic, often referred to as an epidural, is where a local anaesthetic is continually injected through a tube into an area of the lower back called the epidural space. A spinal anaesthetic is a single injection into a similar space in the back. Both types of anaesthetic can be used to numb large areas of the body by stopping pain signals travelling along the nerves in the spine. They can also be used to reduce the amount of general anaesthesia needed during some operations and can provide pain relief afterwards. In some types of surgery, such as knee and hip replacements, they can be used in place of a general anaesthetic. Peripheral nerve blocks. A local anaesthetic (LA) is a drug that causes reversible local anaesthesia and analgesia. When these agents are applied to specific nerve pathways (nerve blocks), they have a range of effects from analgesia alone (sensory block) to a complete motor block with paralysis. Anatomy and physiology of nerve conduction. Individual nerve fibres are made up of an axoplasm and a phospholipid membrane. This membrane contains transmembranous spanning proteins which act as ion channels. The action potential is generated by altered Na<sup>+</sup> permeability across the membrane and lasts only 1 - 2 msec. Electrical An epidural providing a local anaesthetic and an opioid also reduce pain (equivalent to a reduction of 2.5 on a scale from 0 to 10 for pain on movement at 24 hours after surgery) and time spent in hospital for open surgery (equivalent to one day). We found no evidence that an epidural with a local anaesthetic would affect the incidence of vomiting or poor healing of the gut. Quality of evidence. An epidural containing a local anaesthetic, with or without the addition of an opioid, accelerates the return of gastrointestinal transit (high quality of evidence). An epidural containing a local anaesthetic with an opioid decreases pain after abdominal surgery (moderate quality of evidence). We did not find a difference in the incidence of vomiting or anastomotic leak (low quality of evidence). 4. Epidural anaesthesia for caesarean section. The vast majority of the participating hospitals prefer plain ropivacaine 0.75%, followed by ropivacaine and bupivacaine 0.5%, each supplemented with Sufentanil. Other local anaesthetics and adjuvants (fentanyl) do not play an important role as first-line drugs (Table 3). Table 3 Preferred local anaesthetic, concentration of the local anaesthetic as well as preferred adjuvants for epidural anaesthesia in caesarean section. Full size table. 5. Epidural analgesia in spontaneous delivery.