THE CONTROL OF ACUTE POSTOPERATIVE PAIN

R. W. D. MITCHELL AND G. SMITH

In recent years, the special knowledge and abilities of anaesthetists have extended into the fields of chronic pain control and the control of pain in labour. However, acute pain, and particularly the treatment of postoperative pain, has received less attention. Although there is now a surge of interest in acute pain [29], the majority of patients undergoing major surgery still receive techniques of pain relief that have changed little in the past 40 years. This situation pertains despite many advances in the understanding of pain mechanisms, the action of analgesic drugs and the development of sophisticated systems for drug delivery. This review examines recent work on the pharmacology of the analgesic drugs and systems for their delivery, and considers their systemic use in the control of acute, especially postoperative, pain.

Definition of acute pain

There is no clearly defined distinction between acute and chronic pain. In general, acute pain is associated with a distinct disease or injury and it is assumed that the time-course of the pain is limited to the period of repair of the injury. However, some acute pain states may progress to become chronic. This may result from progression of the disease process or from a disturbance in neurophysiology following repair of the original injury.

Acute pain is an extremely complex sensation which extends beyond simple nociceptor input, the central processing of which is modulated strongly by emotive elements such as fear, anxiety or depression and by previous experience of pain. It is difficult to quantify the contribution of these elements in the overall experience of acute pain observed in an individual patient. Although it is easier to regard acute pain as a single sensation, some regard must be paid to the contribution of each factor, despite the difficulty of assessment, because it may influence rational treatment. This can be extremely difficult in practice and may require complex multi-dimensional scoring techniques which are not often appropriate to acute pain and are frequently confined to the treatment of chronic pain.

PSYCHOLOGICAL ASPECTS OF ACUTE PAIN

There are enormous individual variations in patient response to acute pain and this variability is well recognized after surgery. Many clinicians have encountered the occasional patient who requires little or no analgesia even after major surgery, but they recognize that, at the other extreme, there are those for whom it seems impossible to provide adequate analgesia, despite the best efforts of the attendants. These extremes presumably lie at the opposite ends of a distribution curve for susceptibility to pain and it is widely held that psychological variables account for many of the observed differences. As noted above, pain is a complex summation of nociceptive input, emotion, state of arousal, thought processes and social influences. Psychological approaches may be utilized not only to assess the susceptibility of an individual to acute pain, but also as part of rational therapy [9].

Situational stress

The simple event of hospital admission produces a significant stress response. The individual’s response to the strange environment has been shown to correlate closely with subsequent pain perception. Four particular factors were associated: loss of independence, spouse separation, isolation and lack of information.

Pre-existing psychological stress

Three major variables influence the degree of distress of patients undergoing surgery.

Anxiety–Tranquillity. The subjective state of
anxiety can be sub-divided in different ways. "Anticipatory" anxiety is that evident before a forthcoming unpleasant event and "concomitant" anxiety is that associated with the event. Recent work [36] suggests that the two are linearly related, that is, patients who are anxious before surgery are more distressed afterwards. "State" anxiety is that associated with a certain set of circumstances and "trait" anxiety is applied to those who tend to react with strong emotion to any stressful experience. Scott, Clum and Peoples [36] have shown that preoperative state anxiety has a linear relationship with postoperative pain.

Some patients use the defence mechanism of denial as a means of removing the unpleasant feeling of anticipatory anxiety. In doing so, they refuse to think of possible future events of which they are afraid. Thus, although they may have very low anticipatory anxiety scores, they will vary greatly in their concomitant anxiety when confronted with pain. Some may be able to maintain the process of denial throughout, while others may suffer great distress as the stimulus overwhelms the denial mechanism. This obviously depends on the severity of the stimulus and the "coping" abilities of the patient.

Helplessness-active control. Helplessness is well recognized as a major cause of stress. Patients in acutely painful situations often feel powerless to exercise any control over their state. Thompson [42] has identified four components to this:

1. Behavioural control. This describes any manoeuvre which the patient can use to decrease the perception of pain; for example, relaxation or breathing exercises or the provision of a patient-controlled analgesia device.

2. Cognitive control. This comprises the alteration of pain by thought processes. These can act both to reinforce the pain (e.g. by concentration on or re-interpretation of the pain) or decrease the pain (e.g. by denial, dissociation and distraction).

3. Information. Provision of adequate information reduces the uncertainty, and therefore the distress, of a painful experience. Films or videotapes may be useful, particularly in paediatric practice, in familiarizing the patient with an unaccustomed experience.

4. Retrospection. The re-interpretation of a past painful event may alter the current implications of that event. This obviously has less bearing on the management of current acute pain.

Positive and negative feelings. When the patient anticipates great benefit from the proposed operation, he may be more willing to trade short-term discomfort for long-term gain. Where the surgery involves mutilation, confirmation of a poor prognosis or no perceived gain in the patient's mind, the additional anxiety may compound the difficulty of providing postoperative analgesia.

ASSESSMENT OF ACUTE PAIN

Therapeutic manoeuvres in medicine should be monitored by assessment of effect. It is an indictment of the current practice of acute pain control that some measure of the adequacy of the analgesia provided is not obtained routinely. Instead, reliance is placed on subjective assessment by nursing attendants, who have little power to modify an inadequate prescription which is provided by the physician on a "safe guess" basis. Research in pain control has yielded many, often complex, assessment systems. While these are likely to remain largely within the province of the research worker, there is a strong case to be made for applying some of the simpler techniques in everyday clinical practice.

Objective methods of scoring pain have relied upon assessment of biochemical indices such as changes in plasma concentrations of hormones, but these tend to be inaccurate, expensive and not applicable in clinical practice. However, measurement of respiratory function, particularly FEV1 and PEFR, is useful in patients who have undergone thoracic or upper abdominal surgery [8]. Although an experienced observer may be able to make a coarse assessment of the degree of pain suffered by a patient, it is accepted widely that the amount of suffering may only truly be assessed by the individual concerned.

Unidimensional scales

With unidimensional scales, the patient is asked simply to define the severity of the pain itself. In its simplest form, the patient may be asked whether or not he feels pain, without any measure of degree. The lack of sensitivity here is obvious. In many acutely painful situations, a total lack of pain is not an obtainable endpoint. Some description of intensity is therefore necessary. A simple verbal rating scale (VRS), such as "none", "mild", "moderate" and "severe" has been shown to have the best correlation with visual analogue scales (vide infra) and an acceptable degree of variation between individuals. Numerical rating scales allow a greater degree of sen-
Control of acute postoperative pain

Sensitivity. It is believed that they circumvent one of the problems of visual analogue scores, which some find confusing because of the wide freedom of choice presented.

Visual analogue scales (VAS) have now been used widely as a sensitive and valid measure of pain intensity. The common pattern is to use a line 10 cm long with extremes labelled “no pain” and “worst pain imaginable”. However, some patients find them confusing and they do require a certain degree of wakefulness and co-ordination to complete. These disadvantages can be circumvented partly by the use of slide-rule devices, which may be processed electronically. VAS may be more efficient for charting the progress of an individual patient rather than for inter-individual assessment. Pain intensity difference (PID) is the difference in pain score at a time after the administration of a drug compared with the pain score at time 0—before any analgesic was given. Summed pain intensity difference (SPID), the sum of PID over a certain period, gives a useful measure of relative efficacies of treatment over the study period, between different patients or groups.

Multi-dimensional scales

The Magill Pain Questionnaire is a well-established tool which assesses pain under three dimensions: sensory, affective and evaluative. While useful in research and in chronic pain states, it is too cumbersome for repeated evaluations of acute pain states in clinical practice. A simpler method of introducing further dimensions into acute pain scoring is to use VAS ratings for anxiety–tranquillity in addition to no pain–severe pain.

We suggest that, where possible, all patients in acute pain should have an assessment of the adequacy of analgesia. This should be as normal as recording of heart rate and arterial pressure. A simple unidimensional scale (VRS or VAS) would be better than no score at all and would provide the degree of feedback that is lacking in present-day practice.

Pharmacological considerations in acute pain

The burgeoning of knowledge in the neurophysiology and pharmacology of pain in recent years has been spectacular, although this knowledge has yet to have a major impact on the treatment of acute pain for the majority of sufferers.

Pharmacology of the opioid drugs

There have been great advances in two areas in recent years: the understanding of opioid receptors and the development of new drugs acting on these receptors.

Opioid receptor theory

For a fuller description of this topic the reader is referred to excellent reviews by Jordan [18] and Yaksh [46].

In common with other neurotransmitter/hormone systems, it is now known that the opioid system comprises several distinct receptor subgroups and a wide range of endogenous ligands. The physiological significance of the endogenous opioid peptides is not yet fully established, but it is possible that, in the future, synthetic analogues of these substances may be produced and used in the practical management of pain.

The original work of Martin [21] proposed three receptor types: mu, kappa and sigma. Further work in animals has suggested the existence of two other receptors, delta and epsilon, and possibly many others, the significance of which is unclear at present. Table I describes the three main receptor subtypes. Drugs may act as agonists, partial agonists or antagonists at any or all of these receptors. Thus the simplistic description of some of the newer synthetic opioids as

| Table I. Characteristics of the three main types of opioid receptor |
|---------------|----------------|----------------|
| Receptor      | mu             | kappa          | sigma          |
| Analgesia     | Yes            | Yes            | No             |
| Respiration   | Depression     | Depression     | Stimulation    |
| Behaviour     | Euphoria       | Sedation       | Dysphoria      |
| Pupil         | Miosis         | Miosis         | Mydriasis      |
| Morphine      | Suppression    | No suppression | No suppression |
| withdrawal    |                |                |                |
"partial agonists" tends to obscure their true action. Table II illustrates a proposed receptor interaction scheme for some currently available agents.

### Table II. Effects of seven agents on the three main types of opioid receptor. NA = No activity; PA = partial agonist. (Adapted from Rosow [31])

<table>
<thead>
<tr>
<th>Receptor</th>
<th>mu</th>
<th>kappa</th>
<th>sigma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Agonist</td>
<td>Agonist</td>
<td>NA</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>PA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>PA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>Antagonist</td>
<td>PA</td>
<td>Agonist</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Antagonist</td>
<td>PA</td>
<td>Agonist</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Antagonist</td>
<td>PA</td>
<td>Agonist</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Antagonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>

**Pure agonist drugs**

Despite the current availability of several new agonist/antagonist or partial agonist drugs, the pure agonists remain the mainstay of the treatment of acute pain. Morphine is the "gold standard" against which any new drug must be compared.

All opioid agonists produce analgesia, respiratory depression, euphoria, decreased gut motility, nausea and cough suppression, and have the potential to cause urinary retention. In the doses used in normal clinical practice, they produce analgesia without marked depression of consciousness. Unlike most of the agonist/antagonist drugs, however, there is no "ceiling effect" to their analgesia and respiratory depression and very large doses have been used as a sole agent in cardiac anaesthesia; even with these enormous doses, loss of consciousness is not always assured.

Differences between agents result largely from differences in pharmacokinetic profiles or from effects on non-opioid systems, rather than distinct pharmacodynamic effects. For example, the onset time for analgesia with morphine is slower than that with fentanyl because the former has a lower lipid solubility, and the ability to cause histamine release possessed by morphine is absent with fentanyl.

It is well known that there are great variations in plasma opioid concentration profiles after i.m. administration: for example, it has been demonstrated with pethidine that there is a 2–5 fold difference in peak plasma concentrations and a 3–7 fold difference in the rate at which these concentrations are achieved after a single i.m. injection [4]. Thus the pharmacokinetic properties quoted usually for these drugs are those calculated after i.v. injection. Figures for the agents used commonly are shown in table III. These data do not have much bearing on the latency or duration of action of an i.v. dose of the drug—properties which are governed by the lipid solubility and partition characteristics in blood.

All opioids are weak bases and at physiological pH they exist in both ionized and un-ionized forms. Only the unbound and un-ionized form (which is relatively lipid soluble) is free to penetrate lipid membranes, gaining access to the site of action or biophase. This proportion is termed the diffusible fraction and amounts to 16% of plasma morphine, 2.5% of pethidine and 1.4% of fentanyl. However, as stated, the actual lipid solubility of the drugs varies greatly. The octanol:water partition coefficient for morphine (free base) is 6, for pethidine it is 525 and for fentanyl 11220. The product of diffusible fraction and lipid solubility gives the "diffusing potential" into the CNS. Taking morphine to equal 1, the relative ratios for pethidine and fentanyl are 13.6 and 162, respectively [17].

Variations in patient characteristics may lead to wide variations in pharmacokinetic parameters. In hepatic disease, it has been shown that the beta half-life of pethidine is approximately doubled because of decreased drug clearance. The oral bioavailability of pethidine is increased greatly in patients with hepatic cirrhosis, although there is little change with morphine or fentanyl [5].

The extremes of age have a marked effect. In neonates, the terminal half-life of pethidine is several times longer than in an adult. In patients older than 80 yr, the clearance of pethidine is decreased and the volume of distribution is smaller. The beta half-life of fentanyl is twice as long in elderly patients and this has been attributed to decreased drug clearance [5]. Impaired hepatic metabolism or decreases in liver blood flow may be factors in this observation.

Other drugs may affect the pharmacokinetics of opioids. Enzyme inducing agents such as phenytoin or phenobarbitone decrease the terminal half-life of pethidine. By inhibiting hepatic microsomal enzymes involved in oxidative processes, cimetidine impairs the metabolism of both pethidine and fentanyl. As morphine is metabolized predominantly by glucuronidation, its clearance is not affected.
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Table III. Pharmacokinetic properties of some opioid drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial volume of distribution (litre)</th>
<th>Total volume of distribution (litre)</th>
<th>Initial half-life (min)</th>
<th>Terminal half-life (min)</th>
<th>Clearance (ml min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>23</td>
<td>224</td>
<td>1.7</td>
<td>177</td>
<td>1050</td>
</tr>
<tr>
<td>Pethidine</td>
<td>88</td>
<td>305</td>
<td>7.1</td>
<td>222</td>
<td>1020</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>60</td>
<td>335</td>
<td>4.1</td>
<td>185</td>
<td>1530</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>11</td>
<td>27</td>
<td>8</td>
<td>98</td>
<td>238</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>14</td>
<td>188</td>
<td>2</td>
<td>184</td>
<td>1275</td>
</tr>
</tbody>
</table>

It is now well-recognized that the metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are biologically active [13]. A recent study of patients receiving long-term oral morphine medication showed an analgesic ratio of morphine to M6G of 1:10 [27], whereas an earlier study had shown a ratio of 1:2.5 after a single dose [35]. This may partly explain the higher analgesic efficacy of repeated doses compared with single doses, at least in chronic pain. In end-stage renal failure it is known that the terminal half-life for morphine is the same as in normal subjects [1]. Recently, it has been shown that the prolonged duration of action of morphine in these patients may be a result of relative accumulation of M6G [37].

Opioid agonist/antagonists

With pure agonist drugs, increasing the dose generally causes an increase in analgesia and in respiratory depression. Thus the maximum analgesic effect obtainable is extremely high and is obtained with doses well outside those that can be used in clinical practice with spontaneously breathing patients.

Measurement of efficacy is extremely difficult with regard to the agonist/antagonist opioids, largely because dose–response relationships for these drugs are not linear. Indeed, depending on the relative affinities of the drugs in their agonistic and antagonistic effects, the dose–response curve may be U-shaped or bell-shaped. All the available opioid drugs in this class demonstrate a bell-shaped curve in animal studies. This implies a high affinity for the agonistic effect and a low affinity for the antagonistic effect; thus in low drug concentrations the agonistic effect predominates, but in higher concentrations antagonism predominates. If the transition between agonism and antagonism occurs within the clinical dose range, the drug has low efficacy at higher doses for severe pain. This phenomenon has been demonstrated in patients treated with nalbuphine after upper abdominal surgery [28].

The unusual dose–response relationships of these drugs also introduce difficulty in assessing equipotency. Given that the drug under study has a sufficiently high “ceiling” (i.e. that the degree of pain anticipated is not close to the plateau of efficacy of that drug), the standard models of postoperative pain may be used to establish equipotency with a standard agent, for example morphine, in a certain dose. However, because there is no certainty that the log dose–response relationship of the agent studied is linear, statements on equipotency with morphine can be made only in relation to the dose used [19].

Pentazocine. This drug was the first agonist/antagonist to become established in clinical practice. It is presumed to be an agonist at kappa and sigma receptors and an antagonist at mu receptors. Doses of 30–50 mg produce analgesia and respiratory depression to an extent approximately equivalent to that obtained with morphine 10 mg; increasing the dose above this intensifies side effects, but does not increase analgesia. Pentazocine causes an increase in heart rate, pulmonary arterial pressure and cardiac work [2] and is therefore best avoided after myocardial infarction.

The usefulness of pentazocine is limited by the high incidence of dysphoria, hallucinations and bad dreams associated with its administration. The technique of “sequential analgesia” [30], in which pentazocine was used at the end of surgery to antagonize large doses of fentanyl given during operation has not found widespread acceptance.

Nalbuphine. This agent was introduced to the U.K. relatively recently, but has been available in
the U.S.A. for many years. It appears to act as a kappa and sigma agonist and has quite potent mu antagonist properties. Although it is thought to be approximately equipotent with morphine, several studies have shown that it has a low ceiling effect. If adequate analgesia is not obtained with a low dose, waning of analgesia occurs with increasing dosage, although it then causes marked depression of conscious level [28]. Therefore the agent is not recommended for the treatment of severe pain such as follows upper abdominal surgery [12]. It does not possess the deleterious haemodynamic effects of pentazocine when used for the pain of myocardial infarction.

**Buprenorphine.** This agent is thought to act as a partial mu agonist. It appears to have limited efficacy, but an extremely high affinity for the receptor. It has a very high lipid solubility, but its speed of onset is limited by a low diffusible fraction and a rapid decrease in plasma concentration (because of a large total volume of distribution) after a single i.v. dose. Its duration of action is prolonged (5–6 h after i.m. injection). Its potency is approximately 25–50 times that of morphine. High lipid solubility lends this agent a useful property: that of excellent absorption by the sublingual route. If buprenorphine is swallowed, extensive first-pass hepatic metabolism results in a low bioavailability and therefore little danger of overdosage if a patient accidentally swallows the tablet(s). A ceiling effect for respiratory depression has been demonstrated with this agent in animals, but significant respiratory depression may occur with the doses used clinically. The effects of buprenorphine are not antagonized readily by naloxone. Doxapram, a respiratory stimulant, is recommended if significant depression of respiration occurs.

Buprenorphine is relatively devoid of side effects such as dysphoria and hallucinations and causes subjective effects similar to those of morphine. In controlled trials in acute severe pain, the incidence of nausea and vomiting was not significantly greater than that observed with morphine. The often-reported clinical observation that nausea and vomiting are major problems with this agent may simply be a reflection of its widespread use in less severe pain. Because of its extremely high affinity for the mu receptor, there is a theoretical possibility that the effects of pure agonist drugs given during anaesthesia may be attenuated in a patient receiving this drug before operation. Indeed, buprenorphine has been suggested for use in a modern resurrection of the technique of "sequential analgesia" (vide supra).

Buprenorphine is probably the most useful agent among the recently-introduced agonist/antagonists. It is the only one currently available which has been found consistently of value in acute, severe pain.

**Meptazinol.** This agent is unusual in that, in addition to partial agonistic effects at the mu receptor, it appears to act by other mechanisms. The role of these other mechanisms, which are thought to be mediated through cholinergic systems, is not clear in man. It has been shown to be effective in postoperative pain [38] by parenteral administration and has a potency approximately similar to that of pethidine. It is well absorbed rectally, but it has been shown that a dose of 150 mg by this route is not adequate for treatment of pain on the first day following hysterectomy [23]. It is said to have a low potential for respiratory depression and its effects can be reversed with naloxone. However, recent work (Hanning and colleagues, in preparation) has shown that the frequency of episodes of arterial desaturation in elderly patients after hip replacement was similar in patients receiving either meptazinol or morphine by patient-controlled analgesia. Side effects (nausea and vomiting) have been reported to be troublesome in obstetric analgesia and it does cause sedation. However, it causes a low incidence of dysphoria and hallucinations, presumably because of lack of action at the sigma receptor.

**Non-Steroidal Anti-Inflammatory Drugs in Acute Pain**

There is a bewildering number of non-steroidal anti-inflammatory drugs (NSAID) currently available. Although their major use is in chronic pain, there is an increasing interest in their use as adjunctive therapy for acute pain states. The rationale for this is that soft-tissue inflammation may be a potent factor in postoperative pain. However, most of these agents require oral administration and are not usually appropriate for severe acute pain, although some are available as suppositories. While Martens [20] showed that rectal naproxen greatly decreased the requirement for opioids after orthopaedic surgery, work in our department (in preparation) has shown that
suppositories containing diclofenac 150 mg had no morphine-sparing effect after cholecystectomy. However, this agent has been found effective for post-tonsillectomy pain in children [44]. Ibuprofen by suppository has been found to produce a 20% decrease in morphine requirements after lower abdominal surgery [24].

Diclofenac is noteworthy in this group for being currently available in an injectable form (for i.m. use only). This has been shown to be of value in acute renal colic, and has been found to be as effective as i.m. papaveretum after hip surgery [7]. A study in patients after abdominal surgery [15] showed a significant morphine-sparing effect, although the study may be criticized for failing to standardize between upper and lower abdominal surgery.

It seems likely that NSAID will prove more effective for analgesia after orthopaedic surgery than after abdominal surgery. The question of whether or not the well recognized side effects of these drugs (inhibition of platelet function and gastrointestinal irritation) represent significant problems in the management of acute pain can only be answered by large scale studies.

**POSTOPERATIVE PAIN**

This is obviously the area of acute pain control of most interest to anaesthetists. It comprises the largest group of patients suffering acute pain and management has long been recognized as sub-optimal. Its transitory nature, however, should render it more amenable to treatment than chronic pain [39].

**Conventional Therapy**

Treatment has traditionally failed to recognize the complex problems involved. Standard practice is to prescribe i.m. administration of a fixed dose of an opioid on a “PRN” (as required) basis. Thus a dose of analgesic is given, at the discretion of a nurse, on demand by a patient in whom the pain threshold has been exceeded. This type of regimen gives poor results for the following reasons:

1. Responsibility for management of the patient is delegated from the anaesthetist to junior medical staff who, in turn, delegate responsibility to the nursing staff.
2. Nursing staff vary widely in their degree of rapport with the patient and they may be too busy to deal immediately with a request for analgesia. Administration of opioids takes time because of the necessity for checking the drugs according to Controlled Drugs Act regulations. Nurses may withhold opioids because of fear of side effects, particularly respiratory depression, and the perceived potential for producing physical dependence. While there is little evidence to suggest that the treatment of acute pain with opioids for 2–3 days after operation is likely to cause addiction, respiratory depression remains a valid concern.
3. In the absence of personal experience of the severity of postoperative pain, it is difficult for nursing staff to acknowledge the extent of a patient’s suffering in the postoperative period.

Other major difficulties in the treatment of postoperative pain include:

1. Difficulties in quantifying pain (see above).
2. Difficulty in titrating doses of drug to a measured effect—there is no easily defined “endpoint”.
3. Analgesic requirements vary widely according to the type and severity of surgery.
4. Analgesic requirements vary widely as a result of pharmacokinetic and pharmacodynamic variations between individuals.
5. Administration of adequate doses of analgesics may be inhibited because of induction of side effects such as nausea and vomiting or respiratory depression.

Thus the list of disadvantages of the conventional method of administering i.m. opioids is daunting: the dose prescribed may be too small (inadequate analgesia) or too large (side effects); the technique results in widely fluctuating plasma concentrations of the drug; i.m. injections are painful; and the technique induces a feeling of dependency on the nursing staff. There are, however, some advantages of this conventional method. It represents familiar practice and thus may be inherently safe because of accumulated experience. It requires no special equipment and is therefore inexpensive, and the gradual onset of analgesia permits observation of the gradual onset of possible overdose.

**Newer Approaches to Treatment**

**New drugs**

As discussed above, it is unlikely that any of the current agonist/antagonist drugs represents a major advance on pure agonist drugs in most situations. Those with a low propensity for
respiratory depression also have a low "ceiling" for analgesia.

**New methods for old drugs**

These techniques embody the philosophy that established agents are more effective if given in a manner which optimizes their action. To obtain effective analgesia, the aim is to maintain a steady-state plasma concentration of opioid in the region of the "minimum effective analgesic concentration" (MEAC (table IV)). As this varies widely between individuals, it is not possible to predict a dose regimen for a particular patient in advance of some assessment of that patient's susceptibility to opioids. With bolus i.v. and continuous i.v. techniques, the assessment of the patient's requirements is in the hands of the observer. With patient-controlled analgesia (PCA), a feedback loop is established whereby the patient controls his own plasma opioid concentration according to need.

**Bolus i.v. administration.** It is common practice to administer small i.v. boluses of opioid in the recovery room to produce analgesia in the period immediately after surgery. In the setting of the high-dependency area, this technique may be continued in the later postoperative period, and may be acceptable, providing there is a 1:1 nurse:patient ratio, to permit detection of respiratory depression. This technique produces wide fluctuations of plasma opioid concentration which may be lessened by continuous infusion or PCA methods.

If titrating an i.v. opioid against pain in the short term, it is inadvisable to use an agent with a slow onset, such as morphine or buprenorphine, unless the time to maximal effect of each increment (approximately 10 min) is observed before administering a further increment. In situations where rapid control of pain is desired, it is preferable to use an agent with a faster onset time such as fentanyl, diamorphine or pethidine.

**Continuous i.v. infusions.** Various authors have attempted to assess the patient's opioid requirements by means of small i.v. boluses until adequate analgesia is achieved. They then prescribed a fixed continuous i.v. infusion based on the initial quantity of opioid administered [10, 33, 34]. There are several problems associated with this technique, the most important being the potential for overdosage and respiratory depression, particularly if the initial assessment of opioid requirement did not take into account the slow onset of some drugs. More complex regimens have been developed which take into account the complex pharmacokinetics of opioids [3, 17, 40]. In the view of the authors, continuous infusion techniques based on observer control should be used only in high-dependency nursing areas where the inherent problems of respiratory depression can be rapidly diagnosed and treated. It is worth noting that hypovolaemia may cause a relative overdose of opioid if the initial assessment was made when the circulating volume was normal.

**Patient-controlled analgesia (PCA)**

The concept of PCA may be regarded as a simple closed-loop system. Unlike simple infusions, for which the observer determines the plasma concentration of drug, the patient determines the dose required to maintain adequate analgesia. The optimum plasma concentration, as determined by the patient, is that which satisfies his subjective requirement for analgesia while avoiding excessive dosage which would produce unacceptable side effects such as nausea and vomiting or such a degree of CNS depression which would by itself inhibit further activation of the apparatus.

The most basic form of PCA apparatus, such as the original Cardiff Palliator, administers a bolus dose of drug on receipt of a correctly delivered demand. The size of the bolus dose and the "lockout time" (the minimum time interval between doses) is set by the operator. The rate of infusion of each bolus can also be set. A problem with this form of apparatus is that, if the patient falls asleep and thus makes no demand for some time, the plasma concentration of analgesic decreases below the MEAC for that patient and the patient may waken in pain. It may then take several demands to restore adequate analgesia. Even so, it has been suggested that there is less disturbance of nocturnal sleep during PCA compared with conventional therapy [25].

**Table IV. Minimum effective analgesic concentration (MEAC) for some opioid drugs in plasma**

<table>
<thead>
<tr>
<th>Agent</th>
<th>MEAC plasma concn (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>16</td>
</tr>
<tr>
<td>Pethidine</td>
<td>455</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>10</td>
</tr>
</tbody>
</table>
To obviate this theoretical problem, other workers have developed machines which deliver a continuous low-dose background infusion on which the patient may superimpose additional demands for bolus doses. This philosophy was extended even further [17] by Hull in his development of the on-demand analgesia computer (ODAC) apparatus which will give 50% of the demand doses of the previous 1 h as a continuous infusion over the succeeding 1 h, thereby gradually decreasing the rate of continuous mandatory infusion as the patient’s pain state gradually improves.

The problem with all continuous infusion strategies is the possibility of respiratory depression. In the original, experimental ODAC device, a pneumograph monitor was incorporated which inhibited the infusion if there was a 15-s period without respiratory movement. It has not been possible to incorporate this feature in the commercial version of the device. For safety, therefore, it may be best to accept a mandatory infusion rate which falls some way short of maintaining a steady-state plasma concentration close to the MEAC value, and allow supplementation by bolus demand.

The Cardiff Palliator is no longer available and has been replaced in the U.K. by the more sophisticated Graseby patient-controlled analgesia system which, like the on-demand analgesia computer, is a microprocessor-controlled pump which permits a background infusion in addition to patient-demanded boluses; however, the rate of the background infusion is operator-controlled. The philosophy of patient-controlled analgesia and development of apparatus has been reviewed [22, 25].

Efficacy of PCA. Although experience with PCA is expanding rapidly, especially in the U.S.A., its use has not become widespread in routine clinical practice in the U.K. Nevertheless, there are sufficient data to suggest that it represents a major advance in analgesic therapy in postoperative pain. Obviously, not all patients will be suitable for the technique: the very young and those who cannot comprehend what is required need an observer-based technique.

Most workers have reported consistent results with PCA: it has a high degree of patient acceptability and subjects tend to maintain a relatively constant plasma concentration of opioid (although there may be a 4-5 fold difference in concentrations between individuals). Dose requirements are generally smaller than the maximum which would be available if the same drug was given on a PRN basis. There is no suggestion that PCA leads to more side effects such as sedation, nausea or respiratory depression than conventional i.m. analgesia. However, cases of severe respiratory depression as a result of operator or machine error have been reported, and this emphasizes the need for full training in the technique for all staff concerned [35, 39, 41, 45]. Work from our department [43] suggests that the “low dose infusion + bolus” technique with morphine yields marginally better results than bolus alone.

Routes of administration. Most work with PCA has used the i.v. route. It is important that either a dedicated i.v. cannula or a one-way valve is used to ensure that each dose reaches the patient and does not accumulate by retrograde flow into an i.v. infusion. The i.m. and s.c. routes have also been used satisfactorily. Extravascular administration of opioids has also been reported on a PCA basis, but this technique should be confined to high-dependency areas.

Other routes of administration of opioids

Oral. The use of sublingual buprenorphine has been considered above. The oral route of administration of drugs is the most widely used for all types of medication and is often the most acceptable to the patient. However, apart from minor ambulatory surgery and in the late postoperative period after more major surgery, the oral route of administration of opioid analgesics has several major disadvantages:

1. Delay in gastric emptying is common after surgery. Because absorption of these drugs occurs from the small intestine, analgesia may fail because of lack of absorption. More seriously, the dumping of a large volume of drug into the small bowel when gastric motility resumes may result in overdose at a time when the patient may be under less close surveillance. Work with the slow-release tablet formulation of morphine (MST Continus, Napp Laboratories) after abdominal surgery confirms that absorption is delayed within the first 24 h of surgery [26]. Thus the use of this formulation is not recommended within 24 h of surgery.

2. Nausea and vomiting in the postoperative period may preclude the use of oral medication.

3. Because of considerable first-pass metabolism in the liver, the bioavailability of oral opioids is greatly reduced. Prediction of adequate dosage is
thus even more difficult than with parenteral administration.

Although some reports have stated that adequate analgesia may be achieved using this route, the oral route is generally regarded as unsuitable for the administration of strong opioids in the early postoperative period.

**Rectal.** The use of rectal diclofenac and meptazinol has been noted above. Rectal administration of drugs is relatively unpopular in the U.K., but this route does possess some advantages:
1. Absorption of drugs from the lower part of the rectum bypasses the portal venous system. Drugs absorbed in the upper rectum pass into the superior rectal vein and are, therefore, subject to first-pass metabolism. The overall bioavailability may thus depend on the siting of the preparation in the rectum.
2. Absorption of drugs is unaffected by delay in gastric emptying, or by nausea and vomiting.
3. Administration of the drug may be discontinued simply by removal of the suppository.

The rectal route has been used with sustained-release preparations of morphine (the morphine hydrogel suppository) and this technique may be useful in producing a low sustained plasma concentration of the drug which can be augmented by further systemic doses [14].

**Transdermal.** Transdermal administration of drugs is now well established in therapeutics, and suitable delivery systems for glyceryl trinitrate have been available for several years. Recently, a transdermal delivery has been developed for fentanyl, and encouraging results have been obtained in the treatment of postoperative pain [32]. Holley and Van Steennis [16] and Duthie and colleagues [11] reported that the TTS-fentanyl patch (TTS = transdermal therapeutic system) was capable of providing an analgesic plasma concentration of fentanyl. The product is designed to provide a sustained release of 100 μg h⁻¹. However, it should be applied 2 h before the expected painful stimulus and a bolus of i.v. fentanyl is necessary as a loading dose.

**SAFETY CONSIDERATIONS**

Although traditional PRN methods of administering postoperative analgesia may be inadequate, they do have the merit of simplicity and familiarity in use which provide a degree of inherent safety. New techniques and drugs must be shown not to entail any unjustifiable hazard to the patient. When dealing with opioid drugs, the overriding concern of the prescriber is the avoidance of dangerous respiratory depression.

**Monitoring of respiration**

The maintenance of adequate pulmonary gas exchanges is obviously essential to life. Unfortunately, it is difficult to make a simple bedside judgement of the adequacy of ventilation, especially in the sleeping subject.

The work of Holley and Van Steennis [16] confirmed previous observations that random counting of ventilatory rate does not correlate with the presence of hypercapnia. In a study with i.v. and transcutaneous fentanyl, subjects with $P_{aCO_2} > 6.7$ kPa had ventilatory rates varying from 7 to 22 b.p.m.; conversely, in subjects with ventilatory rates of 10 b.p.m. or less, $P_{aCO_2}$ values ranged from 3.3 to 7.1 kPa. Catling and colleagues [10] observed a high incidence of episodes of arterial oxygen desaturation during continuous opioid infusions in postoperative patients and emphasized the need for continuous oxygen administration in these patients: this was found largely to obviate decreases in saturation.

If simple observations do not suffice, what may be utilized? Pulse oximetry detects arterial oxygen desaturation but, in the presence of supplementary oxygen, may not detect mild respiratory depression. Electromechanical strain-gauge devices may be used for continuous monitoring of chest-wall movement, but may not detect the presence of an obstructed upper airway. In practice, however, continuous monitoring with the pulse oximeter is probably the safest method of assessment.

It should be noted that there is some debate on the incidence of significant sleep apnoea in the normal population [6], although there is general agreement that the condition is commoner in males, in heavier subjects and with increasing age.

**THE ACUTE PAIN SERVICE**

The deployment of more sophisticated forms of acute pain relief (local anaesthetic techniques, extradural opioids, PCA) has been constrained by the facts that these techniques may be time-consuming and that correct application requires specialist skills and knowledge. Ready and colleagues [29] have described their experience with an Acute Pain Team to supervise patient-con-
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trolled analgesia and extradural opioid analgesia. It may be difficult to provide a similar service elsewhere because of manpower constraints, but many of the advantages of this type of service could be obtained by greater stratification of patient care in hospital. The provision of high-dependency units, which would concentrate on the provision of care for patients in the immediate postoperative period, would greatly facilitate the use of effective analgesic techniques and may allow the more efficient deployment of nursing and medical staff.

In conclusion, we have attempted to examine some of the recent advances in postoperative analgesia using systemic drugs. Perhaps the most important task we have is to heighten awareness of the size of this problem and to ensure that all staff are aware of the variables involved. Most patients in hospital will continue to receive i.m. opioids because of the simplicity of, and familiarity with, this technique. However, the introduction of simple methods of pain scoring and a greater degree of flexibility in the administration of opioids would lead to considerable improvement in acute pain therapy.

REFERENCES


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