OPIOIDS IN CHRONIC PAIN

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SITE AND MECHANISM OF ACTION

The aim in using opioid drugs in chronic pain is optimal pain relief with a minimum of side effects. A rational approach requires understanding of the clinical pharmacology of opioids given by a variety of routes, for the differences between routes may be greater than the differences between drugs given by the same route. Those using opioids in chronic pain differentiate between their clinical and laboratory pharmacology, a distinction which is not so apparent in acute, operative and postoperative care. The side effects which are perceived as limiting clinical use, such as respiratory depression and dependence liability, are often of minimal clinical importance in chronic use, as long as appropriate doses are used to treat opioid-sensitive pain.

Opioid Receptors

Opioid drugs work as analgesics by binding at opioid receptors in brain and spinal cord. A schematic view of the relationships between the mu, delta and kappa receptor subgroups is shown in figure 1.

Exogenous opioids used in pain management have different binding selectivities on the different receptor subtypes. The functional role of these different endogenous systems is unclear. The mu system has an analgesic effect in both acute and chronic pain, although the endogenous ligand is unknown in certain areas. Enkephalins appear to be the endogenous ligands at delta receptors and blocking the degradation of enkephalins produces analgesia in animal pain models [15]. The mechanisms by which they achieve their effect also appear to be different, mu and delta operating through the potassium channel, kappa via the calcium. Kappa shifts the mu dose response to the right, and this is shown by — in the figure. The relative ability of ligands for the subtypes to achieve maximal analgesia on the dose–response measures is shown by the percentage figures in each section: mu 100%, delta 75%, etc.

Application of kappa ligands does not produce analgesia in all test systems, although effects are seen with systemic administration [32]. Electrophysiological studies with intrathecal doses revealed two types of kappa effect, one decreasing C fibre firing, the other increasing it; the net result was no analgesia [30]. The kappa system may establish the baseline activity on which mu and delta operate. This may be important in chronic pain states.

Two strategies for future development of analgesics were proposed as a result of receptor identification. The first was that analgesia without

side effects might be achieved by use of kappa- or delta-selective drugs. This has yet to be proved clinically. The second was that blocking the degradation of enkephalins might produce analgesia, again without side effects, because an endogenous analgesic was being made to last longer. Blocking degradation is effective in animal models, although the maximum analgesic effect may be considerably less than that achieved by mu agonists [15].

Animal models of chronic pain suggest that the N-methyl-D-aspartate (NMDA) receptors may also be important. Specific NMDA antagonists produce analgesia, as do opioids with anticonvulsant actions [72]. Coherent strategies for future opioid analgesic development for chronic pain may need to focus on this site, because those chronic pains which respond poorly to opioids (see below) are sometimes responsive to anticonvulsant and antidepressant drugs.

Conundrums in Opioid Clinical Pharmacology

The clinical pharmacology of the opioids has some important differences from the effects observed in the laboratory. These differences appear to depend on the presence or absence of opioid sensitive pain when the drug is given. In the presence of such pain, appropriate doses do not lead to the problems of respiratory depression and addiction. These are the two commonest reasons given for limiting prescription, so that understanding of this “dual” pharmacology is of more than just theoretical interest, especially in regard to pain conditions which respond poorly to opioids.

Respiratory depression

It is easy to demonstrate the respiratory depressant effect of agonist drugs in volunteers. In patients with pain, however, clinically important respiratory depression is a rare problem, both after operation and in chronic pain states [69]. The mechanism by which the presence of opioid sensitive pain protects against the respiratory depressant effect is unknown, but is important clinically. Taking a double dose of morphine at night does not cause problems [56], but patients adequately treated with opioids develop respiratory depression if the pain is taken away by a nerve block and the opioid dose is not decreased [22, 35]. The balance between nociceptive input and opioid effect is necessary to avoid respiratory depression. After successful nerve blocks, opioid dosage should be decreased by 75%; further reduction may then be possible over the following weeks.

The mechanism of this balance may be more specific than arousal, which was the explanation given for the phenomenon of greater respiratory effects of opioids in anaesthetized volunteers [19]. Medullary respiratory centre cells with nociceptive input have been demonstrated in the cat [1], and input here may act to balance the respiratory depressant action.

Concern about respiratory depression should not inhibit the appropriate use of opioids, which is to provide analgesia when the pain may reasonably be thought to be sensitive. The corollary is that, when opioids are used for insensitive pain, or in sensitive pain at doses greater than those required for analgesia (as in the ITU to facilitate ventilation of the lungs), or for purposes other than analgesia, such as sedation, then the problem of respiratory depression may be encountered.

Opioid-insensitive pain

In chronic pain it has long been realized that not all pain states are relieved by opioids [34]. A good example is trigeminal neuralgia, in which they provide poor pain relief and the anticonvulsant, carbamazepine, works well. Opioid sensitive pain may be defined as pain which responds progressively to increasingly potent drugs: the corollary is that opioid insensitive pain does not. This distinction is shown by the failure of some patients with chronic pain to distinguish the analgesic effect of i.v. drugs from placebo [3].

Arner and Meyerson [3] assessed the opioid sensitivity in three groups of chronic pain patients: those with “primary nociceptive pain”, those with “neuropathic deafferentation” and those with “idiopathic pain” (little or no demonstrable pathology). Effective relief in nociceptive pain contrasted with lack of response in the other two groups. The paper emphasized the clinical necessity of distinguishing between pathological pain conditions rather than considering them as homogeneous and assuming that the response to opioid treatment will be the same [8].

The commonest causes of opioid insensitive pain are nerve compression and nerve destruction (deafferentation) and the reason may be loss of primary afferent receptors with post-synaptic preservation. The deafferentation pain associated with nerve destruction in cancer patients usually
results from tumour infiltrating the nerve. The painful area may have decreased or altered sensation. An analogous (and also opioid insensitive) pain is seen in post-herpetic neuralgia. Nerve compression may produce a neuralgic pain, often not controlled by opioids, in an area with normal sensation. Other causes of opioid insensitive pain include gastric distension, rectal tenesmoid pain and central pain (thalamic pain; phantom limb pain).

The clinical difficulty lies in patients with pain at more than one site (when that at one site is sensitive and the other is not) or in distinguishing a dose response for mood elevation from one for analgesia. Relative opioid insensitivity may be predicted from history and examination. Management may be pharmacological, with unconventional analgesics (antidepressants, anticonvulsants or steroids [34]), or with nerve block or surgery.

Addiction

The fear of producing addiction is, together with respiratory depression, one of the main reasons for underuse of opioids in treating chronic pain. Addiction, the "...compulsion to take the drug on a continuous or periodic basis in order to avoid the discomfort of its absence" [73], is, like respiratory depression and tolerance, a facet of opioid pharmacology which is rarely a clinical problem.

To determine the incidence of opioid addiction, the Boston Collaborative Drug Surveillance Programme examined the files of nearly 12000 medical inpatients who had received therapeutic opioids. There were only four clear cases of dependence in patients with no previous history of addiction [54]. Such psychological dependence should be distinguished from physical dependence; in the context of successful nerve block the opioid dose may be decreased dramatically, and withdrawal symptoms and signs may follow [29], as can happen in intensive care.

The other complicating factor is the political assumption that medical availability of opioids necessarily increases street addiction. While drug supplies may go astray and be used by street addicts, patients who are prescribed opioids for the management of sensitive pain do not become addicts. To deprive them of this means of pain relief is unjust.

Tolerance

Tolerance may be defined as the need for a larger dose (or greater plasma concentration) to achieve the same pharmacological effect. The word is often misused in pain management to mean an increase in dose; this is only correct if the pain has not increased, and in chronic cancer pain the reason for increasing the dose is usually an increase in the pain [29]. Patients are often maintained satisfactorily on the same oral dose of morphine for months, and this would not be possible if tolerance always occurred.

Genuine tolerance does occur in other contexts. Addicts develop tolerance because they are using opioids in the absence of pain. Acute tolerance has been demonstrated in animal studies: control groups given a painful stimulus before the injection of opioid did not develop acute tolerance [10]. The phenomenon of acute tolerance has also been demonstrated in man [36]. Opioid injection before surgery (before the patient is in pain) is common practice, both as premedication and in the anaesthetic room. It does not create clinical problems because any increase in postoperative drug requirement can be met.

Tolerance to spinal opioid has caused clinical problems in chronic pain management but many of the reports are hard to interpret. In some cases spinal opioids were used for pain which had failed to respond to opioids given by conventional routes. On the basis of this and other clinical criteria, these were opioid insensitive conditions. The second problem with interpretation is in knowing whether the dose being given was the minimum necessary or was more than was needed. If the latter, tolerance would be expected.

The enigma of opioid tolerance reinforces the concept of a dual pharmacology. When the drugs are used in appropriate doses to treat pain which is sensitive, tolerance (like respiratory depression) is not a clinical problem. When opioids are used in the absence of sensitive pain, or in inappropriately high dose when the pain is sensitive, then (like respiratory depression) tolerance can occur.

Indications for Treatment

Patients are often referred to a pain clinic because of failure of conventional analgesic regimens, or because the referring doctor is unwilling to use the dose necessary to achieve analgesia. The use of opioid drugs is only one of the possible approaches (fig. 2) and the first issue in deciding if they are
Is the pain opioid-sensitive? 
Are other measures appropriate? e.g. nerve blocks ± minor analgesics 
Pain from malignancy 
Yes  
No ? Choice of opioid may be limited to mixed agonist-antagonist

Fig. 2. Opioids as one possible approach in chronic pain.

appropriate is that of the sensitivity of the pain (see above). There is little logic in using opioids to treat a pain which does not show a clear dose–response relationship.

Opioids in non-malignant pain

The second issue is that using opioids in non-malignant pain is contentious. The arguments against include the problems of addiction and dependence and the potential long term adverse effects [61]. While there is little evidence to show that these are major risks [18, 53, 64], there are few advocates for the argument that long-term use in such conditions is ideal. The problem remains however, that it may be the only effective remedy. In the small number of patients for whom this is the case, the prescriber should ask two questions: “Is the pain sensitive?”, and “Is there no other effective remedy?”. If the answer to both questions is yes, then the position must be explained to the patient, the family practitioner and the others involved in the patient’s care. The use of drugs such as the partial agonist buprenorphine may be more socially acceptable for this patient group because of the perceived lower dependence liability.

CURRENT PROBLEMS

In addition to tolerance, some of the unresolved clinical issues are the choice of opioid, the decision to prescribe by the clock or as required, and choice of route [18].

Choosing an Opioid

While morphine remains the standard against which others are judged, other drugs may act faster, last longer or have a better balance between effect and side effect for a particular patient. Factors involved in choice of opioid thus include:

- Efficacy and ceiling effect
- Speed of onset and duration of action
- Side effects
- Agonist v. mixed agonist–antagonist
- Prescriber (or institution) preference

It is easy to forget that morphine is not available in many countries of the world because of the political decision that medical availability increases “street” availability. Knowledge of the alternatives is then a necessity. Mixed agonist-antagonists have particular importance in this context because they have lower dependence liability and may be the only permissible agents. For the same reason choice may be limited to this group in non-malignant pain. Drug availability and prescriber or institution preference may thus be the most important determinants of choice.

Efficacy and ceiling effect

When treating chronic pain it is always possible that the pain will increase as the disease pro-
progresses. This affects the choice of drug, because it can be argued that there is no point in prescribing initially an agent which will be incapable of relieving severe pain if the situation deteriorates. The argument is not wholly consistent, because progressive prescribing from non-opioid to opioid is a legitimate strategy, but it highlights the problem of the ceiling to analgesic effect. This is the inability of a drug to relieve pain beyond a certain intensity, despite an increase in dose. One reason that oral morphine has become the standard strong oral analgesic for continuous treatment in cancer pain [66] is that it is effective (with no apparent ceiling) while being relatively safe.

Three types of analgesic ceiling may be distinguished: that from toxicity at higher doses, ceiling as an intrinsic drug property and ceiling from a failure of compliance.

Toxicity. If increasing the dose increases the incidence of unwanted effects, this creates a limit to analgesic efficacy. Codeine and dihydrocodeine are usually classified as “weak” analgesics occupying an intermediate rung on the analgesic ladder. They are inadequate at the greater doses required to control severe pain because of the unacceptable side effects produced with such doses. Similarly, pethidine in large doses (oral doses of 200–300 mg 3 hourly, see below) produces central nervous system toxicity.

Intrinsic drug property. Drugs acting as partial rather than pure agonists may be incapable of relieving severe pain. This may be more of a theoretical than a practical bar to use, because the ceiling effect may occur only at high doses. However, this worry together with fear of negative interaction with pure agonists, has limited the use of mixed agonist–antagonists (see below) in cancer pain.

Failure of compliance. If the dose of drug in each tablet (or ml of solution) is small, and the dose required is large, it may be physically difficult for the patient to take the necessary dose.

Speed of onset and duration of action

Fast onset of effect is not a critical factor if the patient is receiving regular medication, but may be relevant for the patient taking a drug according to need. Several drugs have faster onset times than morphine (table 1).

Alternative oral opioids might also be said to have advantages over morphine if their analgesic effect lasted longer, because fewer doses would be needed each day. At least three alternatives do last longer than morphine. The long plasma half-life of methadone after a single dose (table 1) is out of step with the duration of its analgesic effect, so that it is more difficult than morphine to use effectively and safely. There has been a great deal of confusion because of the disparity between the effect half-life and the kinetic half-life, for methadone and for other drugs. Patient self-titration with methadone is one method to achieve safe use [59]. Levorphanol also has a long plasma half-life (12–16 h), and an analgesic effect duration of 8 h. Buprenorphine has a duration of effect of 8 h, but is a partial agonist. However, the advent of sustained release formulations of morphine means that there is now less reason for choosing another opioid on the grounds of longer duration of effect.

Sustained release formulations. Although the drugs with longer kinetic half-life such as methadone can be titrated safely by patients [59], the

Table 1. Onset time, time of peak effect, half-life and duration of relief with opioid drugs. (Adapted from [65])

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Peak (min)</th>
<th>$T_{1/2}^B$ (h)</th>
<th>Duration of relief (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextromoramide</td>
<td>10–20</td>
<td>60–90</td>
<td>?</td>
<td>2</td>
</tr>
<tr>
<td>Pethidine</td>
<td>40–60</td>
<td>60–120</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Morphine</td>
<td>60</td>
<td>60–90</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>15–30</td>
<td>45–60</td>
<td>?5</td>
<td>4</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>20–60</td>
<td>60–120</td>
<td>12–16</td>
<td>6</td>
</tr>
<tr>
<td>Phentazocine</td>
<td>20</td>
<td>45–60</td>
<td>?</td>
<td>6</td>
</tr>
<tr>
<td>Dipipanone</td>
<td>45–60</td>
<td>90–120</td>
<td>?</td>
<td>6</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>60–120</td>
<td>120–240</td>
<td>3.5</td>
<td>8</td>
</tr>
<tr>
<td>Methadone</td>
<td>30–60</td>
<td>30–120</td>
<td>15/48</td>
<td>8</td>
</tr>
<tr>
<td>MST</td>
<td>120</td>
<td>180 +</td>
<td>(3)</td>
<td>12</td>
</tr>
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only real advantage appears to be fewer daily
doses than with morphine in solution, and
effectively a fixed dose schedule still operates.
This advantage has been minimized with the
advent of sustained release formulations of mor-
phine which also decrease the number of doses
required daily. These preparations are formulated
to release morphine over a prolonged period
(12 h). Clinical experience and controlled studies
have both shown that twice daily dosage substi-
tutes for the same total daily dose of morphine
sulphate solution taken 4-hourly, and for many
patients twice daily doses are more convenient.
One disadvantage is that the time to maximum
plasma morphine concentration is longer than is
found with oral morphine sulphate solution
(approximately 4 h compared with 1–2 h).

Specific side-effects and metabolism
If an opioid has no specific advantage over
morphine and has a specific disadvantage, such as
a troublesome side-effect not found with mor-
phine, then there is little logic in choosing that
drug in preference to morphine. Given equivalent
analgesic potency, any drug which produced fewer
side effects than oral morphine would be an
improvement. For most clinically important side
effects such as constipation or nausea, there is no
comparative evidence from chronic pain patients
to suggest that any of the alternatives produces
fewer side effects while providing equivalent
analgesia. The evidence from single-dose post-
operative studies shows a higher incidence of
nausea and vomiting with pethidine [45], and
dysphoria (see below) with those mixed agonist–
antagonists which have a relatively high affinity
for kappa and sigma receptors [68].

Dysphoria. This occurs with all opioids, but the
incidence varies widely between drugs. There is
little sense in using one which produces a higher
incidence of dysphoria than morphine without
any compensating advantage. Pentazocine, butor-
phanol and nalbuphine have this potential [24].
The greater than 20% incidence seen with
pentazocine and butorphanol contrasts sharply
with the 3% incidence seen with other opioids;
drugs which produce this high incidence have no
place in the management of chronic pain.

Toxic metabolites. Pethidine is metabolized to
norpethidine, which is toxic [63]. It causes
unwanted CNS changes, tremor, twitching, agi-
tation and convulsions, and the incidence of these
problems increases considerably at doses above
200–300 mg, and in the presence of impaired renal
function [7, 63]. Together with its short duration
of action (2–3 h (table I)), this makes pethidine a
poor choice for the management of chronic pain.

Active metabolites. Recent work on dia-
morphine, on the metabolites of morphine and on
the method of excretion has some important
clinical implications. Of the drugs shown in figure
3, diamorphine [28] and morphine-3-glucuronide
(M3G) [9] do not bind to opioid receptors,
whereas 6-monoacetylmorphine, morphine, mor-
phine-6-glucuronide (M6G) and normorphine
do. Quantitatively, the most important active
metabolite is M6G, because M3G and M6G are
the major metabolites of morphine in man [6, 58]
and because of the greater potency of M6G
compared with morphine. In rats, M6G is 45
times more potent than morphine intracerebrally
and nearly four times more potent subcutaneously
[60]; intrathecal injection gave potency ratios
between 10 and 20 [62]. M6G may contribute
substantially to the analgesic effect of morphine,
in both single and repeated doses [20, 39, 50].

Diamorphine is a classical “pro-drug”. Devoid
of analgesic activity itself, it initiates the “cas-
sade” into the active 6-monoacetylmorphine,
morphine and M6G (fig. 3). Because of the speed
of these reactions, there is no clinical advantage
over morphine by oral or i.m. routes, in terms
either of greater analgesic efficacy or of improved
mood [28, 67]. This does not exclude advantage
from i.v., spinal or other routes.

The major advantage of diamorphine over
morphine is solubility. This is relevant when
injections of large doses are necessary, because
they can be given in a small volume. This may also
make diamorphine a logical choice when large
doses are necessary for subcutaneous infusion.

Renal function
Unexpected degree and duration of effect can
be obtained with morphine and its congeners
when they are used in patients with severely
impaired renal function [37]. Cumulation of M6G
is the probable explanation for this phenomenon.
Prolonged respiratory depression has been re-
ported in man in association with negligible
plasma concentrations of morphine, but with very
high concentrations of M3G and M6G [49]. The
relevance of this problem to chronic pain man-
OPIOIDS IN CHRONIC PAIN

Dose equivalence

When changing between the oral and the parenteral route, the dose of morphine must be adjusted, but the exact ratio for the change is not known. In one study the effect of a single injected dose was six times that of an oral dose [25]. In the multiple dosing context of chronic pain, ratios of 2:1 or 3:1 are used successfully [66].

The discrepancy between a ratio of 1:6 with single doses for acute pain and 1:2 or 1:3 with repeated doses for chronic pain has led to much confusion. Both are correct within their clinical contexts. The explanation for the discrepancy may be that active metabolites contribute more to the analgesic effect with repeated doses than with a single dose [21, 39]. An important clinical point is that patients differ, both in the bioavailability of oral morphine (15–64%, mean 38% [58]), and in the effect of the drug, so that individual titration is necessary.

Mixed Agonist–Antagonists

These drugs combine the ability to act like morphine (agonist activity) with potential antagonist activity. Common to the group are lower dependence liability than is found with agonists and a ceiling to their efficacy.

These properties come from the presumed activity of these drugs on more than one opioid receptor type. The simplest (and clinically most important) way of classifying these drugs is into those which are morphine-like, because of partial agonist activity at the mu receptor (buprenorphine), and those which are more similar to nalorphine (pentazocine, butorphanol, nalbuphine), with agonist action on the kappa receptor.

The classification is clinically important because, whereas morphine-type drugs predictably have subjective and physiological effects like morphine, and do not cause a higher incidence of psychotomimetic reactions than morphine, the nalorphine-type of mixed agonist–antagonists cause increased incidence of psychotomimetic reactions (see above) and this limits their usefulness in chronic pain.

The ability of these drugs to antagonize other opioids has led to the dictum that they should not be prescribed together with agonists. This antagonist ability is, however, far from straightforward, first because antagonism is more evident with chronic exposure [27], and second because
many patients who have been prescribed both agonist and partial agonist drugs at doses within the "normal" therapeutic range, appear to have additive analgesia [33]. While co-prescription makes little sense, because it invites problems unnecessarily, the disparity between the clinical observations and the pharmacological predictions remains to be explained satisfactorily.

The issue of ceiling to efficacy appears to be restrictive in chronic pain only for nalbuphine (ceiling equivalent to morphine 30 mg); for buprenorphine the ceiling has been estimated at 5 mg day\(^{-1}\) [77], at which point compliance is more likely to be a limiting factor. Two benefits of efficacy ceilings are that the ceiling for respiratory depression appears to be equivalent to approximately 20–30 mg of morphine, making the drugs theoretically safe in overdosage. Theoretically there should also be a ceiling to constipation.

Prescribe Regularly or as Required?

Should opioids be given on a fixed "by the clock" schedule or when the patient asks for them? The rationale for the safe and effective hospice teaching that the fixed dose schedule for oral morphine is best is that such schedules prevent the pain re-emerging. If this is allowed to occur, the relatively slow onset of analgesic effect of oral morphine means that it takes time to re-establish control. Sustained release morphine formulations may have an even slower onset time, and hence be even more ineffective.

While there is no inherent merit in allowing the pain to re-emerge in this way, some patients feel "drugged" when taking oral morphine on a fixed dose schedule, and would prefer to take the drugs when needed. Others require additional rapid onset pain relief for pain which breaks through background analgesia. Unfortunately, the kinetic and dynamic profiles of the alternative oral opioids do not offer much advance over oral morphine. Faster onset of analgesic effect is required for on-demand use, and this is claimed for dextromoramide and levorphanol (table I), and for morphine hydrochloride compared with morphine sulphate. A regimen may be tailored with background control with morphine and a faster onset oral opioid in addition, either to enable patients to titrate their pain relief against any clouding of thought or to control unpredictable break-through pain.

Alternatively, judicious use of non-steroidal anti-inflammatory drugs or paracetamol may be used to get round this problem, adhering then to the purist philosophy of only prescribing one opioid at a time. Combining the effects of aspirin and opioid produces an additive increase in analgesia [26], known as the opioid-sparing effect because greater analgesia is achieved without increasing the opioid dose.

Route of Administration

Thirty years ago many doctors did not believe that oral opioids were effective analgesics, despite centuries of use. Now that the oral route is the accepted standard for chronic cancer pain, novel routes are being explored to improve pain relief and to minimize side effects.

Two clinical issues have become confused in discussion of alternative routes. The first is clinical necessity; some patients may have to be managed by a "non-standard" route of administration, such as those cancer pain patients who cannot take oral medication. The overall proportion of patients in this category is not known, but is likely to be greater in a pain clinic or hospice because referral will follow failed oral treatment. The second is the potential of novel routes to provide better analgesia or fewer side effects than standard routes, so that the novel route supplants the standard. The current problem is providing cogent clinical evidence to confirm these potential benefits [16].

The sublingual and spinal routes are discussed in some detail because they are current clinical alternatives to conventional routes of administration. Other proposed routes (nasal, transdermal, inhalation, etc.) should be subject to the same questions: what is the kinetic logic of the route, and what is the clinical logic?

Sublingual and buccal opioids

Kinetic logic. The kinetic logic behind using the sublingual and buccal routes is that the drug is given without injection, but is absorbed systematically (analogous to an i.m. dose), avoiding any first-pass effect. Circumventing this increases relative systemic bioavailability, but the real clinical gain is that it should make the effect of a given dose more predictable both within and between patients than an equivalent oral dose. It is the variability of the first-pass effect which makes short-term use of oral opioids difficult. An additional gain of faster onset of analgesic effect
was anticipated by analogy with other drug classes used sublingually (15 min for anti-angina drugs).

Sublingual buprenorphine provides the best example of the kinetic gain in availability. After operation, 0.4 mg sublingually produced analgesia equivalent to that obtained with 0.3 mg i.m. Relative systemic availability was 55% (range 16–94%). The relative systemic availability of oral buprenorphine, in contrast, was about 15% [38, 71]. Substantial gains in onset time for analgesic effect have not been found; 30 min is the accepted time in chronic use.

The kinetic advantage of sublingual use would be predicted for high clearance drugs with a substantial first pass effect when taken orally, but not for low clearance drugs. No advantage for sublingual use of methadone, which has a low clearance and high oral availability, would be expected and none was found [38]. Similarly, little kinetic advantage was found with sublingual morphine [38, 51, 71], and recent work with buccal morphine [4] had no oral controls, so that no advantage over oral relative systemic availability could be shown.

Little is known about the influence of formulation and physico-chemical properties of drugs, such as lipophilicity, on sublingual and buccal availability. Manipulating the drug formulation may maximize the availability and minimize problems of taste and local irritation; it will not change the logic that avoiding the first-pass effect is an advantage only for high clearance drugs which are subject to a substantial first-pass effect. Such manipulation might also result in a faster increase in plasma concentrations and hence produce faster onset of analgesic effect; this advantage would apply to both high and low clearance drugs.

Clinical logic. Sublingual use is an alternative for patients in whom swallowing is difficult, and when a drug can produce analgesia as good as could be achieved by injection. Sublingual buprenorphine produces analgesia equivalent to parenteral doses. This advantage should be considered particularly when potent opioids are needed in contexts where injection is most problematic: in children, in subjects with haemophilia or in patients who cannot swallow. The agonist drug phenazocine has also been used sublingually [5], but there are no comparisons with the use of oral morphine.

Subcutaneous injection

Injection of opioids is necessary when a patient cannot swallow medication, cannot absorb it or has persistent vomiting. The choice of drug for parenteral use may be dictated by consideration of the volume to be injected, particularly if repeated injections have to be given in cachectic patients. Diamorphine is much more soluble than morphine (100 mg will dissolve in 0.2 ml) and is used widely in Britain for this purpose. The dose given for injection is half the orally effective dose of diamorphine (30% of the orally effective dose of morphine). Morphine acetate and hydromorphone hydrochloride are alternatives.

Subcutaneous infusions using a battery-driven portable syringe driver [48] may be useful for the patients (e.g. those with inoperable bowel obstruction) who need longer term parenteral medication.

Intravenous use

Hospitalized patients and those with long-term central venous cannulae may be managed with i.v. bolus or infusion, and the route has been used successfully in the young [42, 43].

Spinal Opioids

Giving opioids by spinal (a generic term for intrathecal and extradural) routes in chronic pain management is contentious, for it has potentially greater morbidity than conventional routes. The importance of spinal opioids is the potential for a quality and duration of pain relief greater than that achieved with conventional routes. This potential puts spinal opioid use in the category of novel routes for which the risk:benefit ratio compared with conventional routes must be defined [16]. The belief that applying opioid directly into central nervous system (CNS) produces an absolute difference in incidence of analgesia and side effects compared with conventional routes has little logic behind it; the drugs act on the same receptors however they are given, so that the difference can be only relative. Spinal opioid use in chronic pain has had a strong phenomenological flavour. The appropriate clinical role is not resolved.

Kinetic logic

Spinal administration uses injection of exogenous neurotransmitters close to the CNS to work directly on the receptors. The kinetic problems of
conventional routes, such as uncertain absorption into, and delivery by the circulation to, CNS sites, are hence circumvented. The process, however, substitutes a different set of problems. The principles which underlie the systemic kinetic differences between drugs, such as the influence of lipophilicity on the ability to cross the blood–brain barrier [23], are circumvented by direct spinal application [40]. This is evident in the potency of different mu agonists given i.v. or intrathecally. Methadone 10 mg given systemically produces analgesia equivalent to that from systemic morphine 10 mg. Intrathecally, however, the ED$_{50}$ for methadone is 18 times that of morphine [40]. These differences between systemic and spinal dose requirements have not been applied as they should have been in determining equianalgesic doses.

The benefit of giving opioid extradurally as opposed to using conventional parenteral routes comes from the fraction of the extradural dose which crosses the dura directly. While the kinetics of this fraction will be predictable from intrathecal kinetics, the proportion of drug absorbed systemically will follow the kinetic principles for systemic absorption. Taking the example of methadone, the "systemic" fraction is equipotent with morphine, but the "spinal" fraction is not, because of lipophilicity. This additional complexity has not been addressed adequately.

The high drug concentrations achieved after lumbar intrathecal injection [44] spread rostrally [46], and make a combination of spinal and supraspinal effect possible. This may be a necessary combination for adequate analgesia. Systemic absorption from the extradural space would also take drug to supraspinal receptors. The high CSF concentrations, however, also raise the spectre of toxicity, which may be of particular importance if spinal opioids are to be used in non-malignant pain. None has been found, either in prolonged studies in monkeys (4–16 months extradural morphine [75]), or in man after 6 months extradural morphine [41]. Both dural thickening after chronic intrathecal administration [12] and pain on extradural injection [76] are attributable to disease rather than to the spinal opioids. The use of the more potent agents should perhaps be recommended, on the basis of fewer non-specific actions, until more is known.

**Clinical logic**

**Analgesia.** For chronic pain there is evidence that a small dose of drug given spinally can provide analgesia equivalent to that from larger doses given orally or by conventional injection routes. The duration of effect of these smaller doses may also be greater. There is little comparative evidence for a lower incidence of side effects.

Opioids are often administered spinally in chronic pain when they have failed by conventional routes. This presumes that the failure is based on the drug not reaching the receptors in the CNS so that, if it is given directly, analgesia will ensue. Unfortunately, it is difficult to be sure from the literature that reports of success or of failure are reports of patients who fulfil this criterion. Overall, the proportion of patients for whom conventional routes fail is low (? 15%), and the majority of these have pain at one or more relatively opioid-insensitive sites.

The crucial issue is whether or not the pain is sensitive, because there is no point in using opioids if it is not [2], and even less point in delivering them by a route which has a high morbidity. Sensitivity may be determined using the i.v. route [3], or by double-blind comparison between intrathecal opioid and saline [17]. Most sensitive pain can be managed successfully with oral administration, so the high morbidity spinal route is appropriate only if the pain is sensitive and conventional routes are contraindicated. The suspicion remains that spinal opioids can produce a better quality of analgesia with fewer side effects than conventional routes, but this is not proven. If this suspicion were to be confirmed, then the balance of the equation would be tipped in favour of more widespread use of the spinal route in patients managed currently with opioids given by conventional means.

A simple method of converting from the conventional route is to try 1% of the total daily dose as the daily intrathecal dose, and 10% as the extradural dose [11]. Initially, the intrathecal dose may be given once daily and the extradural dose twice. The doses used in chronic pain (0.05–1 mg [70]) may be increased as disease or tachyphylaxis develop [2]. There is no comparative evidence to recommend infusion rather than bolus administration, or to prefer constant infusion to systems with which additional demands can be met as in patient-controlled analgesia. Efficacy of low dose extradural infusions [14] suggests that the dose response for infusions may be different (response at lower doses) from that for bolus injection. If, at
these low doses, the same quality of analgesia is provided with fewer side effects, infusion may be preferable. It is unclear whether or not the same is true for intrathecal administration. The overriding principle is to balance the dose and the pain. If infusions contravene this rule, the incidence of side effects is increased and tolerance will develop if a dose greater than that required for pain relief is given. If low dose infusion is preferable, the infusion must be “tailored” to the pain.

**Intrathecal or extradural?** The intrathecal route offers certain availability of the drug in CSF when compared with the extradural route. Spinal availability is a function of drug lipophilicity and there is variability between drugs. Technical difficulties with extradural injections and catheters cause variability between and within patients. There is an analogy to the certain availability of the i.v. route when compared with the i.m.

Intrathecal administration requires dural puncture, and the relative merits of repeated puncture against an intrathecal catheter [70] must be considered. The advantage of implantable intrathecal catheter systems is claimed to be a lower infection rate. The disadvantages are the extra logistic difficulty and the cost. Again, not all chronic pain is relieved by spinal opioids [2], and caution must be exercised before “leaping in” with an implanted system. Intraventricular catheters were used effectively for tuberculosis treatment and may have considerable advantage over long-term lumbar catheters, the usefulness of which may be limited by problems with CSF leakage and catheter maintenance [70].

An extradural catheter might be thought to have considerable logistic advantage and produce less morbidity than an intrathecal one, but there is no comparative evidence. The long-term (more than 1 year) use of extradural catheters in this context has been shown to be effective [13, 78], but with problems of obstruction, kinking, removal and infection. Tunnelling the catheter may reduce infection, but does not appear to reduce the incidence of the other complications [11]. The advantages of implanting injection reservoirs or systems remains to be seen. These “high-tech” approaches have often been used in patients with insensitive pain, making the results (other than logistic success) uninterpretable.

**Side effects.** The major problems encountered in acute pain are itch, urinary retention and respiratory depression. In chronic pain these have not been problematical [11]. The reason is not that chronic pain per se protects against these phenomena, but rather that previous opioid exposure seems to minimize the incidence. Comparisons of the incidence of side effects of chronic oral and chronic spinal administration are lacking. Anecdotally, patients whose use of oral morphine was restricted by side effects have had analgesia without side effects when spinal opioids were used. Comparisons of the incidence of side effects with different opioids given chronically by spinal routes are also lacking. Both types of comparison will require equianalgesic doses to be established.

The development of tolerance to spinal opioids (that is the need for larger doses to obtain the same effect), has been seen often in the treatment of chronic pain. Tolerance developed faster when opioid was infused spinally than when bolus injections were made on demand [17], but the problem is not insuperable, because increasing the dose defeats the tolerance. Temporary abstention has the same effect, presumably related to the advent of new (previously unexposed) receptors. The reason that tolerance develops faster with infusion than does demand may be that infusion at higher than necessary dose predisposes to development of tolerance (see above).

**PRACTICAL PRESCRIPTION OF ORAL ANALGESICS**

Two concepts underlie the sequential use of analgesics, “by the ladder” and “by the clock” [74]. In chronic pain of increasing severity, analgesics of increasing strength are used sequentially—ascending the ladder. In acute pain weaker analgesics are used as the pain intensity decreases—descending the ladder.

The standard non-opioid analgesic is aspirin. Paracetamol may cause fewer side effects and prove equally effective, despite a lack of anti-inflammatory activity. Non-steroidal anti-inflammatory drugs are more powerful analgesics than either aspirin or paracetamol, and may become the first line treatment. The archetypal weak opioid is codeine, but the combination of dextropropoxyphene with paracetamol is preferred by many patients because of lower incidence of side effects, particularly constipation. The standard strong opioid is morphine.

The concept of regular “by the clock” administration was discussed above. For codeine and morphine (“normal” formulations) a 4 hourly
regimen is optimal. A 6 hourly prescription may be satisfactory for levorphanol, phenazocine or methadone (table I).

The following guidelines are suggested:

**Non-opioid and weak opioid.** With mild or moderate pain, use a non-opioid initially. If relief is inadequate, add a weak opioid, and titrate the dose against effect. Simultaneous prescription of two weak opioids makes no sense. If increasing the dose of the chosen drug does not relieve the pain, a strong opioid should be prescribed, rather than waste time by prescribing an alternative weak drug.

**Strong opioid.** Oral morphine should be used when the less potent drugs fail to control the pain despite regular use at an appropriate dose. The aim with opioid responsive pain is to titrate the dose of analgesic against the pain, increasing the dose appropriately until the patient is pain-free. The effective dose varies from patient to patient and from time to time; the correct dose for the patient is that which gives good pain relief for at least 4 h without unacceptable side effects. The range of morphine doses used is between 5 mg and 1000 mg 4 hourly, emphasizing the difference between patients; most never need more than 100 mg, and many need considerably less, the median 4 hourly dose of oral morphine sulphate solution being 10 mg [66].

The starting total daily dose of oral morphine for most patients whose medication is being changed from a weak opioid is 60 mg/24 h to 90 mg, to 120 mg, to 180 mg, to 240 mg and to 360 mg. Opioids should not be used without thought for constipation [55]. The use of anti-emetics as a routine is contentious. Initial nausea and drowsiness after commencing therapy with a strong opioid often decrease after about 3 days, and many patients never need an anti-emetic.

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