Pain Control in Advanced Cancer: Pharmacological Methods

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Pain is a major symptom in some 60 per cent of patients managed in a general oncology unit[1] and up to 85 per cent of patients referred for hospice care[2]. Pain control is therefore an essential component of the modern management of malignant disease.

Pain is a complex subjective experience, combining the perception of a painful stimulus with a variable emotional response to it. Chronic pain associated with progressive malignancy is quite different from acute pain following trauma or surgery, or the minor acute pains (headache or toothache) of normal day to day life. Unlike acute pain, chronic pain is of unpredictable duration and is maladaptive: it has no positive function. Thus a major component of chronic cancer pain is the associated emotional reactions of fear, anxiety, anger or depression. Invariably the patient is also troubled by other symptoms such as anorexia, nausea, constipation, fatigue and sleep disturbance, all contributing to a lowered pain threshold and impaired pain tolerance. The clinical picture of the patient with chronic cancer pain is a summation of the physical effects of the original nociceptive stimulus, the patient’s emotional response to this, and other symptoms associated with the underlying malignancy or caused by the pain. The situation is further complicated by the fact that 80 per cent of patients in pain will have more than one pain and approximately 20 per cent will have four or more separate pains[3].

Management of Chronic Cancer Pain

As the nature of chronic cancer pain is so complex it is necessary before embarking upon treatment to identify each individual pain and its underlying aetiology, to appraise the patient’s mental state and to evaluate any associated physical symptoms. A body chart is often helpful and will also provide a valuable baseline for future assessments.

Once the underlying nature of the patient’s pain has been identified a logical treatment strategy can be devised. The mainstay of treatment will be pharmacological. It is, however, important not to neglect the role of other treatment modalities and at this early stage to identify those pains which may respond to specific non-drug measures, such as the use of radiotherapy for localised bone pain.

A further important step at the outset of treatment is careful explanation to the patient and reassurance that pain control can be achieved. Realistic goals should be set, with three stages of pain control in mind: to be pain free at night, pain free at rest and pain free on movement. The first two of these will almost always be possible to achieve and confidence will be built up as each objective is realised. Complete pain control on movement may be more difficult and sometimes simple modifications to life style, in addition to specific treatment, are needed.

Drug Treatment of Chronic Cancer Pain

Effective drug treatment is founded on the regular use of an appropriate analgesic given in an adequate dose. Initial choice of drug is based on the severity of the pain and its response to previous treatment. In general, a simple scheme using a limited number of drugs familiar to the prescriber is recommended, ranking drugs according to analgesic strength with a range from simple non-opioid analgesic, to weak opioid, to strong opioid. One drug in each class should be used routinely, for example paracetamol, dextropropoxyphene/paracetamol, and morphine; only rarely will an alternative be necessary. If a drug is no longer effective there is no value in using alternatives from the same group, and it is inappropriate to use two drugs of similar strength in the hope of an additive or synergistic action. Proprietary tablets containing combinations of drugs, in particular those combining several simple analgesics, are best avoided unless careful consideration has been given to the individual constituents and their doses.

There is no place for intermittent ‘as required’ analgesia in the management of chronic cancer pain. The aim of treatment is to control and prevent further symptoms by regular medication, maintaining constant effective blood concentrations in the steady state. A recommended scheme of drug use in chronic cancer pain is outlined in Table 1.
Table 1. Recommended scheme of drugs for use for chronic cancer pain.

| Pain                        | Mild pain                                      | Unresponsive to simple analgesics | Unresponsive to weak opioids |
|-----------------------------|-----------------------------------------------|-----------------------------------|------------------------------|
| Analgesic group             | Simple peripherally-acting analgesic          | Weak opioid                      | Strong opioid                |
| Drug of choice              | Paracetamol 1 g 4-hourly                      | Dextropropoxyphene/paracetamol 2 tabs. 4-hourly | Morphine or diamorphine orally 5-200 mg 4-hourly |
| Alternative drugs           | Soluble aspirin 600-1200 mg 4-hourly          | Dihydrocodeine 30-60 mg 4-hourly | Phenazocine, levorphanol, oxycodeone suppositories |
| Drugs to avoid              | Compound preparations                         | Pentazocine                       | Short-acting opioids, combinations, opioids with cumulative toxic effects |
| Other measures              | Co-analgesic                                  | Co-analgesic                      | Co-analgesic                 |

Simple Analgesics

Paracetamol is the preferred simple analgesic where no anti-inflammatory action is required. A derivative of para-aminophenol, it has analgesic and antipyretic effects similar to those of aspirin at equivalent doses up to 1 g. Paracetamol is rapidly absorbed from the small bowel but hardly at all in the stomach: hence gastric emptying may significantly affect the overall rate of absorption. Peak plasma concentrations are reached at 30 to 60 minutes after a single oral dose[4]. In addition to tablets a suppository for rectal use is available for those patients unable to take drugs by mouth. The plasma elimination half-life is 1.5-3.0 hours[5], and regular 4-hourly oral administration of 1 g (two tablets) is the recommended dose.

The principal advantage of paracetamol over other simple analgesics is that it is well tolerated by most patients with no gastric irritant effect. Serious toxicity is not seen when it is used in the above doses. The alkylating metabolite responsible for hepatotoxicity in overdosage is produced only in small amounts at normal therapeutic doses and is rapidly detoxified by conjugation with reduced glutathione[6].

Alternative simple analgesics are not usually required since intolerance to paracetamol is unusual. Failure of a simple analgesic to control pain is an indication for a drug with a stronger analgesic action.

Aspirin (acetylsalicylic acid) is recommended by some authors[3] as the simple analgesic of choice. It has the advantage, in high dosage (4-6 g/day), of additional anti-inflammatory action which may be of value, particularly in the treatment of bone metastases. However, side-effects, including gastric intolerance and metabolic disturbances, are much more common at these doses and the use of one of the newer non-steroidal anti-inflammatory drugs is generally preferable when an anti-inflammatory action is required. At low doses aspirin has no advantage over paracetamol and is generally less well tolerated.

Weak Opioids

These drugs are recommended where simple analgesics are ineffective or in mild to moderate visceral pain which often does not respond to paracetamol.

Dextropropoxyphene/paracetamol (Coproxamol) is our drug of choice in this group, despite continued controversy over its efficacy and potential dangers[7,8]. Dextropropoxyphene is a synthetic opioid structurally related to methadone and a weak opioid agonist. It is readily absorbed from the gastrointestinal tract with peak serum levels at about two hours after administration. The mean elimination half-life is about 15 hours with steady state levels being reached after three to four days of regular 6 to 8-hourly administration. In elderly patients the half-life may be very long (over 50 hours)[9]. Dextropropoxyphene undergoes extensive first pass metabolism, its principle metabolite being norpropoxyphene which also has analgesic activity and a longer half life (about 23 hours) than dextropropoxyphene itself. This metabolite therefore accumulates in plasma[10]. Both dextropropoxyphene and norpropoxyphene reach plasma concentrations in the steady state which are five to seven times greater than those found after the first dose.

It follows from this that studies using single doses of dextropropoxyphene are assessing a very different situation to that which exists in the steady state during regular administration for chronic pain[11]. This may explain why extensive clinical experience with a dextropropoxyphene/paracetamol combination in patients with chronic pain due to malignant disease and in patients with rheumatic disorders[12] suggests that the preparation is effective and well tolerated, but controlled clinical trial data are conflicting. There is, however, substantial evidence to support the efficacy of dextropropoxyphene itself[13] and a single published controlled study in rheumatology patients[14] which indicates the superiority of a dextropropoxyphene/paracetamol combination over paracetamol alone.

The recommended dose is up to two tablets of Coproxamol 4-hourly (each tablet contains dextropropoxyphene 32.5 mg and paracetamol 325 mg). At these doses serious side effects are unusual but confusion, dysphoria and lightheadedness may occur, particularly in the elderly. Nausea and vomiting are infrequent and constipation is less troublesome than with other opioids. Addiction has been reported[15] but is rare and does not arise in the treatment of chronic pain. Coproxamol will potentiate the effects of warfarin, carbamazepine and central nervous system depressants.
Alternative weak opioids should be restricted to pure opioid agonists such as codeine or dihydrocodeine. Dihydrocodeine is probably the alternative drug of choice being a semi-synthetic analogue of codeine and approximately 30 per cent more potent than the parent drug. Both drugs are chemically closely related to morphine (codeine is 3-methylmorphine). After an oral dose of codeine some 10 per cent is converted by demethylation to morphine, which may contribute to the analgesic effect. The principal disadvantage of codeine or dihydrocodeine compared with Coproxamol is that they tend to be more constipating at equi-analgesic doses[3].

Pentazocine is a mixed opioid agonist and antagonist which, although in common use, is not recommended for chronic pain due to malignant disease. It is a derivative of phenazocine, a strong opioid agonist. An evaluation in patients with chronic pain[16] showed an analgesic potency of one sixth that of morphine, and another single dose study[17] has suggested that standard doses are less effective than standard doses of dextropropoxyphene with paracetamol. Thus no clear advantage of pentazocine exists in terms of analgesic efficacy and there are two major drawbacks; first, it may antagonise opioid agonists and, second, there is a high incidence of psychotomimetic effects, occurring in 20 per cent of patients in one series[18], half of which resulted in a major disturbance.

Strong Opioids

When pain is no longer controlled by a weak opioid in standard doses, then a strong opioid should be used in its place, titrating the dose to the patient’s pain. Morphine sulphate is the drug of choice for oral use, most readily taken in aqueous solution or in chloroform water as morphine elixir. Morphine is the pharmacologically active constituent of opium. Despite its widespread use, dating from the third century B.C., accurate data on the pharmacokinetics of morphine are sparse, primarily due to the difficulties in measuring morphine distinct from its metabolites in serum[19]. Absorption from the gastrointestinal tract occurs readily (mainly in the upper small bowel) but oral bioavailability varies considerably (between 15 and 64 per cent in one study in cancer patients[20]). The effect of an oral dose is significantly less than that of the same dose given intravenously due to a considerable first pass effect. In rats, 85 per cent of an oral dose is eliminated due to metabolism in both gut wall and liver[21]. While a role for the kidney has been recently proposed[22], the relative importance of renal glucuronidation is disputed[23]. Almost certainly the metabolism of morphine is principally hepatic, the main pathway resulting in the formation of morphine-3-glucuronide and morphine-6-glucuronide. The elimination half life also shows considerable variation from one to 7½ hours after low single oral doses in cancer patients[20], although it is not clear how this relates to steady state conditions after chronic high dosage. During chronic dosing, accumulation of the main metabolites occurs, the average ratio for morphine-3-glucuronide to morphine being 35:1 and for morphine-6-glucuronide 4:1[24]. There is evidence to suggest that morphine-6-glucuronide also has significant analgesic activity[25]. The presence of high concentrations of morphine-6-glucuronide may explain the apparent increased sensitivity to morphine of patients with renal impairment and the possible misinterpretation of kinetic data obtained using an assay method which could cross react with this metabolite[26, 27].

Despite the variation in plasma half-life, in clinical practice regular 4-hourly administration provides constant analgesia in doses ranging from 5 mg to 200 mg every four hours, although occasionally much higher doses are required. The dose is titrated to achieve pain control and around 70 per cent of patients will not require more than 30 mg 4-hourly[28]. The need for a dose to be given in the middle of the night can usually be avoided by a double dose at bedtime.

The use of a slow release preparation of morphine sulphate (MST Continus) has gained increasing popularity over recent years. Peak concentrations of morphine in the blood are not achieved until up to four hours after administration[29], but there are claims that overall bioavailability may be better than with 4-hourly oral morphine sulphate[30]. Although a useful means of delivering regular morphine in a stable situation, it is important to emphasise that this preparation should not be used for acute exacerbations of pain, nor, because of uncertainty over the time to achieve steady state plasma levels, is it ideal for patients starting morphine or requiring regular dose adjustments. MST does appear to be effective when given twice a day, and used appropriately it allows a more convenient regimen for patients requiring long-term morphine therapy[31].

The principal side effects of morphine in chronic use are drowsiness, constipation, nausea and vomiting. Most patients experience drowsiness initially which may cause considerable concern for both patients and relatives, particularly if associated with confusion. However, this is usually transient and not an indication to reduce an effective pain-relieving dose of morphine, but rather should be dealt with by careful explanation and reassurance. Constipation is universal and regular laxatives such as Dorbanex (containing a faecal softener, poloxamer, and a peristaltic stimulant, danthon) should be given from the outset. Nausea and vomiting are not inevitable, up to one third of patients receiving regular oral morphine requiring no anti-emetics[32]. In those patients who do become nauseated, haloperidol taken once or twice daily is usually effective with fewer side effects than the phenothiazines. Where a more sedative anti-emetic is required, prochlorperazine or chlorpromazine taken 8- or 4-hourly is suitable.

Other reported side effects, including pupillary constriction, biliary spasm, increased bladder tone and peripheral vasodilatation, do not usually present a clinical problem in chronic cancer pain patients. Respiratory depression does not occur in patients who are in pain[28] and is not a justification for using inadequate doses.

Addiction does not occur in patients receiving long term opioids for chronic cancer pain. Addiction is based on three separate components: physical dependence, psychological dependence and habituation (Fig. 1). Despite prolonged treatment with high doses of opioids
neither psychological dependence nor habituation is seen. Tolerance to the physical effects of opioids may occur and physical dependence may develop after continuous use for periods of longer than about two weeks. Despite this, in patients whose pain improves or resolves, dose reductions and discontinuation of the opioid may be achieved without difficulty[3].

*Fig. 1. The components of addiction.*

Diamorphine (diacetyl morphine) is the strong opioid of choice for use by subcutaneous or intravenous administration, and may also be substituted for morphine orally. It is a semi-synthetic derivative of morphine and is rapidly deacetylated in the body to monoacetyl-morphine and morphine. Its onset of action after intravenous injection is more rapid than that of morphine and it is associated with less vomiting and less sedation. There is some evidence that diamorphine is better absorbed from the gastrointestinal tract than morphine. However, diamorphine is essentially a prodrug for morphine, diacetylmorphine and monoacetylmorphine being undetectable in blood after an oral dose[33]. Diamorphine has no unique advantages or disadvantages for the relief of pain[34, 35] and its effects are indistinguishable from those of morphine when given 4-hourly for chronic pain[36].

The principal advantage of diamorphine lies in its much greater degree of solubility, enabling high doses to be administered by injection in small volumes suitable not only for intravenous use but also for subcutaneous injection or infusion. The limit of solubility is about 400 mg/ml although a concentration of 250 mg/ml (25 per cent w/w) is probably the maximum that should be used for continuous subcutaneous infusion[37].

It is important to consider the differences in bioavailability when changing from an oral morphine preparation to parenteral diamorphine, dividing the oral dose of morphine by three to obtain an equivalent parenteral dose of diamorphine. Because of the better oral bioavailability of diamorphine, an oral dose of diamorphine should be divided by two to obtain the equivalent parenteral dose.

**Alternative Strong Opioids**

None of the alternative strong opioids possess particular advantages which make them preferable to oral morphine or parenteral diamorphine. Commonly used drugs in this group are shown in Table 2 together with their equivalent oral morphine doses. As can be seen, some are considerably more potent than morphine and this can cause problems in changing from one to another.

*Table 2. Alternative strong opioids.*

| Drug         | Dose (mg) | Oral morphine sulphate equivalent dose (mg) |
|--------------|-----------|--------------------------------------------|
| Buprenorphine (Temgesic) | 0.2*      | 10-15                                      |
| Dextromoramide (Palfium)    | 5         | 10                                         |
| Dipipanone (Diconal when combined with cyclizine 30 mg) | 10        | 5                                          |
| Nerpethine 1ml (10ml of 10% solution) | 12        |                                            |
| Papaveretum (Omnonop)       | 10        | 5                                          |
| Pethidine                | 50        | 6                                          |
| Phenazocine (Narphen)      | 5         | 25                                         |
| Methadone (Physeptone)     | 5†        | 5†                                         |

*Usually given 8-hourly; the equivalent dose of morphine indicated is a 4-hourly dose.
†In single doses only; due to accumulation considerably more potent in chronic usage.*

Buprenorphine is a partial opioid agonist which means that it may have both agonist and antagonist effects. It may be given sublingually or by injection. In acute pain postoperatively it appears effective, but in chronic use it has a high incidence of side effects, in particular nausea and vomiting, dizziness and drowsiness[38]. This limits its effective dose range and together with its potential antagonist action outweighs the advantage of sublingual absorption which may in any case be delayed and unreliable in patients with malignant disease who frequently have dry sore mouths.

Dextromoramide is a potent analgesic but usually has an effective duration of action of only 1½-2 hours. It is unsuitable for the treatment of chronic cancer pain.
Dipipanone has no specific advantages and the important drawback of being available only in a fixed dose combination tablet containing dipipanone 10 mg with cyclazin 30 mg.

Nepenthine used to be an alcoholic tincture of opium but is now formulated almost entirely as morphine hydrochloride[39]. Since it can be made up in various strengths this can cause confusion as to the equivalent dose of morphine and it has no advantages over morphine sulphate.

Pethidine is a synthetic opioid agonist which is generally shorter acting than morphine, its duration of effective analgesia being two to four hours. Its other main drawback for chronic use lies in its conversion to norpethidine by N-demethylation. Although this metabolite does not reach detectable levels after a single dose of pethidine, it accumulates with chronic usage, particularly where there is renal impairment[40]. The elimination half-life of norpethidine is about 17 hours compared with 3.5 hours for pethidine[41]. Norpethidine differs from pethidine in its effects on the central nervous system, having predominantly excitatory effects which are manifest in patients by tremor, twitching, agitation and convulsions. Clinically significant accumulation of norpethidine is seen with doses of pethidine greater than 200-300 mg given 3-hourly, and at lower doses when there is renal impairment.

Methadone is marginally more potent than morphine in single doses. When given regularly, however, its half life increases considerably, with cumulation; plasma concentrations may take two to three weeks to reach a steady state[42]. Furthermore, no clear relation exists between plasma levels and analgesic activity. This tendency to cumulation in regular use can be particularly troublesome in the debilitated and elderly in whom sedation, confusion and, occasionally, respiratory depression may be seen.

Opioid mixtures have been advocated in the past, based on the traditional ‘Brompton Cocktail’, and the current British National Formulary[43] still contains four such formulations containing morphine or diamorphine with cocaine in a sweetened alcoholic base. Use of such cocktails confers no advantages but has a number of disadvantages. The inclusion of cocaine appears to increase side effects particularly in the elderly, and the use of any combination preparation reduces flexibility in dosage.

**Route of Administration**

The majority of patients will have their pain well controlled on oral medication until the final hours or days of their illness, and over 50 per cent will never require an injection[44]. Some patients, however, will be unable to tolerate oral drugs, because of nausea and vomiting, general debility, or impaired consciousness.

Rectal administration is a good alternative but may be unacceptable to some patients. Morphine suppositories are given 4-hourly in the same dose used by mouth and are widely available in a range of strengths. Oxycodone suppositories are an alternative which have the advantage of a longer duration of action (6 to 8 hours). Oxycodone 30 mg is equivalent to morphine 20 mg.

As discussed above, when parenteral medication is required, diamorphine is preferred. The optimum means of administration is by subcutaneous infusion using a syringe driver which avoids the need for repeated skin punctures. An anti-emetic such as haloperidol can be included in the subcutaneous infusion if necessary.

Parenteral opioid analgesics are not inherently better than oral medication when given in equi-analgesic doses, and in practice the indications for the use of subcutaneous infusions are relatively limited.

**Co-analgesics**

A co-analgesic is any therapeutic agent which may not have intrinsic analgesic activity but which will contribute significantly to pain relief when used with a conventional analgesic[45]. Table 3 gives some common examples.

| Drug | Type of pain |
|------|-------------|
| NSAID | Musculoskeletal pain, e.g. bone metastases or soft tissue infiltration. |
| Corticosteroid | Raised intracranial pressure |
| | Nerve root compression |
| | Soft tissue infiltration |
| | Hepatomegaly |
| Diuretic | Lymphoedema |
| (+ compression sleeve, massage) | |
| Antibiotic | Infected ulcer |
| | Discharging sinus |
| Muscle relaxants | Muscle spasm |
| Anticonvulsants | Nerve root pain |
| | Post herpetic neuralgia |

Non-steroidal anti-inflammatory drugs (NSAIDs) do not have a place as primary therapeutic agents but when used in conjunction with an opioid may be very effective particularly in the relief of bone pain. Prostaglandins are involved in peripheral nociceptive mechanisms, sensitising free nerve endings to pain-inducing vasoactive amines and kinins and hence facilitating pain transmission. They are also specifically involved in the development of bone metastases, stimulating osteoclastic bone resorption. Some tumours produce prostaglandin-like substances which may promote their metastatic potential in bone; the use of a prostaglandin synthetase inhibitor has a rational basis in the treatment of bone pain.

NSAIDs have a considerable potential, however, for producing adverse effects particularly on the gastrointestinal tract and in elderly patients[46]. It is important to closely monitor the therapeutic response of each patient and discontinue the drug at an early stage if no clear-cut benefit is seen. Despite a wide range of drugs in this class, none appears to have specific advantages in this indication. Soluble aspirin 600-1200 mg 4-hourly, may be appropriate for patients receiving 4-hourly morphine. In general, drugs which require less frequent administration are preferable for other patients, such as piroxicam 20 mg nocte or flurbiprofen 100 mg b.d.
Benorylate is an ester of paracetamol and aspirin which can be administered as an oral suspension. It has fewer side effects than aspirin used alone and has the additional advantage of 12-hourly dose intervals. It is de-esterified in vivo, each gram of benorylate producing 600 mg aspirin and 440 mg paracetamol. It may be a suitable alternative in certain patients where gastrointestinal tolerance is a problem with anti-inflammatory doses of aspirin, or with other NSAIDs. A dose of 10 ml (4 g) b.d. is equivalent to 4.8 g/day of aspirin.

Corticosteroids are of use in headache due to raised intracranial pressure, nerve root pain due to compression or tumour infiltration, and may also reduce pain due to soft tissue infiltration. Dexamethasone has advantages over prednisolone because of its weaker mineralocorticoid (salt and water retaining) effects, with a lesser tendency to cause oedema and weight gain.

Diuretics may be useful in conjunction with massage and compression for painful lymphoedema.

Antibiotics are helpful for pain from an infected ulcer or discharging sinus, and for dysuria due to a urinary tract infection.

Muscle relaxants are indicated where pain is due to increased muscle tone, spasm or clonus. Baclofen 5–20 mg three times daily is the preferred drug, having less sedative action than diazepam. Some patients, however, have intolerable gastrointestinal side effects and in these diazepam 2 to 5 mg t.d.s. may be used as an alternative. Anticonvulsants may be helpful in some patients with lancinating or stabbing dysesthetic pains associated with nerve compression or infiltration, and post-herpetic or post-traumatic neuralgias. Carbamazepine 100 mg t.d.s., sodium valproate 200 mg t.d.s. or clonazepam 0.5–2.0 mg once or twice daily, may all be helpful. Individual patients may respond better to one particular drug. Clonazepam tends to cause more sedation and the choice of drug should be tailored to the individual patient.

Conclusion

The principles of effective pain control are: make a diagnosis; individualise the treatment; and keep it simple. Familiarity with a simple analgesic ladder will facilitate rational changes in analgesic and dose modifications as appropriate. Predictable side effects such as constipation should be prevented. The appropriate use of co-analgesics including non-drug treatments such as radiotherapy or nerve blocks should also be considered. With this approach it should be possible to control pain in almost all patients with malignant disease without the need for exceptional measures.

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