Use of morphine for cancer pain

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- Used correctly, oral morphine is a reliable, safe, and effective analgesic in patients with advanced malignant disease. It is the oral opiate of choice for terminal pain.

This paper describes the current use of morphine at St. Christopher's hospice, London. Morphine has been used at the hospice as the drug of first choice for chronic pain in advanced cancer since 1977 and more than 2,000 patients have been given it, principally for pain.

Brompton cocktail

In the latter part of the 19th and early 20th century, Sirs Snow, and later Roberts, at the Brompton hospital, London, introduced a mixture of morphine and cocaine to be given orally as a post-thoracotomy analgesic. The “Brompton cocktail” was in common use in Great Britain by the 1930s. The term is now used in a generic sense to describe a solution containing alcohol, opiate (usually morphine or diamorphine), cocaine, and/or a phenoxyamine. Such mixtures are losing popularity to a simpler solution of morphine sulphate in chloroform water, which is equally effective.

The addition of cocaine has not been found to be of extra benefit in clinical studies and alcohol is now given only if individually desired.

Morphine and diamorphine

Pain is the most common (75 per cent) symptom on admission in patients with advanced cancer and morphine is now the oral opiate of choice for its treatment in Britain. In 1981, 77 per cent of patients admitted to St. Christopher’s hospice were given morphine orally at some point during their stay (Table 1).

Lasagna concluded that there was little to choose between morphine and diamorphine and that was confirmed in a crossover study in advanced cancer and by clinical experience. There is no evidence to support the view that diamorphine is superior for routine oral use, nor is there any need for diamorphine to be legalised in those countries in which it is at present unavailable for this purpose.

Stability of morphine solution

The suggested shelf life of a preparation containing chloroform (0.25 per cent) as a preservative is up to two months unopened in ambient temperature and not more than two weeks for partially filled containers and those “in use”. Using double strength chloroform water (approximately 0.5 per cent chloroform) increases the (opened) shelf life to four weeks. Chloroform is a gastric irritant and toxic effects may occur if taken in excess of 0.3ml/24hrs; it is contraindicated in patients with renal, hepatic or cardiovascular disease. Even allowing for the loss of chloroform after frequent opening, the risk of unwanted effects in a patient receiving regular strong analgesic mixtures is a serious consideration and requires investigation. It is possible that the chloroform water contributes to the side effects at the dose rates experienced by patients taking analgesic mixtures and its use should be reviewed.

Canada banned the use of chloroform in drugs for human use from January 1, 1978. Chloroform water helps to disguise the bitter taste of morphine, but cordial or alcohol may be added if desired by the patient to render the medication more palatable. Stability studies on morphine solution made up in water (without the addition of chloroform as preservative) are currently being planned at St. Christopher’s.

Dosage

The normal morphine dose range used is 2.5mg to 180mg four hourly, although in exceptional circumstances a larger dose may be needed. Chronic pain requires constant relief, and as morphine given orally is well absorbed with peak blood levels after 1-2 hours it should be given four hourly. Each dose is normally dispensed in a volume of 10ml irrespective of the size of the dose, i.e., a patient may have 5mg in 10ml or 180mg in 10ml. A patient on four hourly aqueous morphine will thus receive 50 to 60ml in 24 hours; that is normally acceptable to the patient and practical for those administering the medication.

The four hourly regime consists of 5 to 6 doses per 24 hours, i.e., 0100, 0500, 0900, 1300, 1700 and 2100 hours. Provided that a patient is pain controlled (or pain free) and does not normally wake in the night, because of pain it is possible to omit the 0100 dose. Some patients may receive an increment to their normal dose at bedtime (0100), with or without a hypnosedative, to aid a restful and pain-free sleep. A flexible prescribing regime for inpatients, e.g., “30 or 45mg four hourly”, enables nursing staff to alter the dose without delay or recourse to a doctor if a patient’s pain pattern should change, which increases patient confidence, lowers the pain threshold and strengthens the patient/nurse relationship. Dosage should be individually titrated against pain (see Table 2) because of the wide variations in morphine metabolism between different individuals. An aqueous preparation is easy for most patients to swallow (Table 3) particularly the elderly and those with dysphagia, who may have difficulty swallowing tablets.

Oural administration preferable

Oral administration of morphine is effective in 85-90 per cent of patients with pain from advanced cancer provided that it is given as a four hourly regime. It is obviously preferable to repeated intramuscular injections, and may be taken until shortly before death in the majority of patients. It has been found that 70 per cent of patients (Table 4) never require more than 20mg morphine four-hourly irrespective of the duration of treatment. Liquid phenothiazines such as prochlorperazine can be added and do not affect the stability of morphine (the mixtures should not be made up in advance).

If reductions in dosage are indicated, decrements are in general the same as the increment steps. It is possible to discontinue morphine altogether if appropriate by stepwise reduction in dosage without any problems. Even when abrupt withdrawal has occurred in...
error, withdrawal symptoms are mild and do not mimic those seen in drug addicts.

Transfer from other opiates Morphine and diamorphine are clinically indistinguishable in analgesic efficacy and side effects when used in equiagonidal doses. When transferring from one to the other (Table 5) the ratio used is diamorphine 1:1.5 morphine (orally), i.e., 10 mg diamorphine is equivalent to 15 mg morphine. When parenteral analgesia is required (terminally, or for a patient who is vomiting) diamorphine is preferred because it is highly soluble requiring only a small volume for injection (smaller than an equivalent dose of morphine). Parenterally, the ratio is diamorphine 1:2 morphine (intramuscular). Hydromorphone is a suitable alternative to diamorphine and unlike diamorphine is available in the USA.

When starting a patient on morphine the initial dose depends mainly on the patient's previous medication and level of pain. Initially, dosage should be reviewed at least every 24 hours. If a patient is in severe pain an initial dose of intramuscular or subcutaneous diamorphine may be given, followed by regular oral morphine. If "breakthrough" pain occurs between regular morphine doses, paracetamol or dextromethorphan (orally) or diamorphine (IM SC) are suitable, depending on the severity of pain.

Morphine pharmacokinetics Metabolism of morphine after oral administration is largely in the liver and intestinal wall with enterohepatic recirculation and excretion of glucuronide metabolites by the kidney. During therapeutic administration at the dosage described, plasma levels are in the 0-100 nanomol/ml range; wide inter-individual variations in metabolism have been shown during repeated oral administration. Metabolism is route-dependent because of the pre-systemic elimination after oral administration; despite that, repeated oral administration can produce morphine plasma levels comparable to those found after parenteral administration.

Side effects

Adverse effects of opiates are similar when the drugs are used at equiagonidal doses. Tolerance is not a problem, i.e., there is no progressive or irreversible increase in dosage. Patients may be physically dependent but do not become "addicts"; usually patients requesting more analgesia are simply still in pain and require an increased dosage.

Constipation The combined effects of low residue diet, inactivity, dehydration and morphine therapy invariably lead to constipation, which is the commonest side effect of opioids. It should be anticipated by routine administration of peristalsis-inducing agents and stool softeners. Modification of dietary intake, i.e., fillets, bread, may help. A bowel check every third day and use of an enema or suppositories as indicated should alleviate the problem.

Nausea and vomiting Nausea and vomiting are more common in females and in those who are mobile. Some patients experience nausea precipitated by morphine, presumably because of direct stimulation of the chemoreceptor trigger zone (for emesis) in the medulla. A phenothiazine may be necessary prescribed to begin with, e.g., prochlorperazine 2.5 to 5 mg four hourly. Chronic use of antiemetics is, however, unnecessary in most patients and they may be withdrawn after four or five days when the patient has adjusted to morphine therapy. If nausea and vomiting persist, pain control may need to be provided parenterally and drug therapy reassessed. Alternative causes of gastrointestinal upset such as drug interaction, raised intracranial pressure, hypercalema, intestinal obstruction and constipation should be considered.

Respiratory depression When morphine is titrated against the patient's pain and given orally four hourly, chronic ventilatory failure or depression is neither common nor severe; that view is supported by research and extensive clinical experience in a number of centres. Fear of respiratory failure should not inhibit the use of adequate doses of oral opiates to relieve pain in the terminally ill.

Sedation Sedation is usually a transient problem during the first few days of morphine therapy. If it persists the addition of a small dose of amphetamine may be helpful. Sometimes it is necessary to have a "trade-off" allowing a small degree of pain so that the patient is not sedated, as many find this intolerable.

Alternative indications for morphine

Cough and diarrhoea may be relieved by morphine. The drug is also valuable in the relief of dyspepsia, one of the most distressing symptoms of the dying and often associated with pain, e.g., in carcinoma of the lung. The euphoriant effect after oral use is unpredictable and if it occurs it is transient.

Adjuvant drug therapy

Morphine is not a panacea and should be used in the context of a therapeutic programme. Most patients with advanced cancer are multi-symptomatic and need polypharmacy (Table 6). Adjuvant drug therapy can be invaluable in the control of pain, but it is necessary to be aware of drug interactions, which can be favourable or unfavourable (Table 7), and to review therapy regularly.

Phenothiazines Phenothiazines are anti-emetic but are also sedative and co-analgesic. Their use as anxiolytics can be beneficial to the patient but the extent of their co-analgesic effects is unclear and requires further investigation. Drugs commonly used are prochlorperazine, chlorpromazine and methotrimeprazine.

Corticosteroids Corticosteroids, e.g., dexamethasone and prednisolone, are widely used in cancer pain arising from a variety of causes including raised intracranial pressure, nerve compression and extensive soft tissue infiltration. They are also beneficial for their non-specific effects on mood, anxiety and weakness.

Non steroidal anti-inflammatory drugs NSAIDs are valuable in pain caused by bone metastases, either used alone or in combination with morphine. Those most commonly used are aspirin, indomethacin, flurbiprofen and ibuprofen.

Antidepressants It is well known that pain can be caused or exacerbated by depression and will improve with antidepressant treatment; the incidence of clinical depression in advanced cancer is about 30 per cent. Antidepressants are also thought to have an independent analgesic effect although that has never been confirmed by clinical trial.

Sedatives Severe anxiety, confusion and terminal restlessness are some indications for the use of sedatives, but assessment of the underlying causes is essential, and non drug management of the problem should be implemented.

Table 4: Maximum individual dose (four hourly) of morphine prescribed in 524 patients

<table>
<thead>
<tr>
<th>Individual Dose (mg)</th>
<th>Total</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>21.6</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>21.8</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>50.2</td>
</tr>
<tr>
<td>37</td>
<td>1</td>
<td>55.3</td>
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<tr>
<td>52</td>
<td>1</td>
<td>70.8</td>
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<tr>
<td>62</td>
<td>1</td>
<td>82.6</td>
</tr>
<tr>
<td>92</td>
<td>1</td>
<td>98.2</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 5: Equivalent analgesic dosage of commonly used opiates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Route</th>
<th>Frequency (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>100</td>
<td>PO</td>
<td>4</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>60</td>
<td>PO</td>
<td>4.6</td>
</tr>
<tr>
<td>Codeine</td>
<td>50</td>
<td>PO</td>
<td>6</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>IM</td>
<td>6</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>30</td>
<td>PO</td>
<td>4</td>
</tr>
<tr>
<td>Phenazone</td>
<td>50</td>
<td>PO</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 6: Adjuvant drugs used for symptom control in patients with advanced cancer (n = 676)

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoctizines</td>
<td>87</td>
</tr>
<tr>
<td>Constrodes</td>
<td>67</td>
</tr>
<tr>
<td>Night sedation</td>
<td>54</td>
</tr>
<tr>
<td>Anticancer</td>
<td>64</td>
</tr>
<tr>
<td>Daytime sedatives</td>
<td>64</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>64</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>64</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>64</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>8</td>
</tr>
</tbody>
</table>

*excluding phenoctizines

Table 7: Drugs which may have clinically significant interactions with morphine

<table>
<thead>
<tr>
<th>Anticholinergics (minor and moderate side effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoctizines</td>
</tr>
<tr>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Methotrimeprazine</td>
</tr>
<tr>
<td>Ticlopride</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>Opiates (megachloramid)</td>
</tr>
<tr>
<td>Opiates (megapromazine)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

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ed where possible. In most cases over-
sedation is undesirable for the patient and
upsetting to relatives. Methotrimeprazine is
the drug of choice for terminal restlessness in
the last stages.

**Hypnotics** The short-acting benzodiazepines
are preferred, as they do not cause much
daytime sedation, e.g., temazepam.

**Morphine slow release tablets**

Morphine is now available in Britain as a 12
hourly slow release tablet for use in chronic
administration.

A recent controlled study at St Chris-
topher’s hospice compared the slow release
formulation with the conventional four hourly
liquid in patients with pain due to advanced
cancer. There was found to be no difference in
analgesic efficacy or side effects between the
two preparations when used on a mg/mg basis
over 24 hours.

On the basis of those results, we now
recommend that the majority of patients
should be stabilised on the four-hourly mix-
ture and then be transferred to the slow-
release tablets, given 12 hourly at the same mg
dosage per 12 hours.

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