Review article

Oral Morphine in Chronic Cancer Pain

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Summary

Extensive clinical experience has been obtained in the use of opiates during the last decade in special units devoted to symptom control in advanced cancer. Important contradictions have emerged with the clinical pharmacological literature on opiates calling into question its relevance to the treatment of chronic pain. Specifically in the case of morphine it is clear that: it is a very effective analgesic given orally, dosage must be individualized, parenteral use or exotic analgesic 'cocktails' are usually unnecessary, and tolerance, dependence and respiratory depression are rarely common or serious problems which prevent effective pain control provided morphine is used appropriately in accordance with its pharmacological characteristics. Heroin is a suitable alternative to morphine (particularly for intramuscular administration) if differences in milligram potency are taken into account, but has no advantages in terms of either analgesic efficacy or side effects. This paper summarizes clinical experience in the use of oral morphine for cancer pain at St. Christopher's Hospice, any data from clinical investigations which support this approach, and comments on the areas of controversy which have emerged.

Introduction

Morphine has been the oral opiate of choice in use at St. Christopher's Hospice since 1977; more than 1700 inpatients have been given the drug principally for

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1 Supported by DHSS Grant No. OCS (A) 3.
TABLE I
COMMON SYMPTOMS IN PATIENTS WITH ADVANCED CANCER

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>69</td>
</tr>
<tr>
<td>Anorexia</td>
<td>64</td>
</tr>
<tr>
<td>Weight loss</td>
<td>59</td>
</tr>
<tr>
<td>Weakness</td>
<td>49</td>
</tr>
<tr>
<td>Constipation</td>
<td>45</td>
</tr>
<tr>
<td>Dyspnœa</td>
<td>42</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>36</td>
</tr>
<tr>
<td>Oedema/effusion</td>
<td>30</td>
</tr>
<tr>
<td>Cough</td>
<td>29</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27</td>
</tr>
</tbody>
</table>

chronic severe pain. Oral diamorphine (heroin) was used until a controlled trial [20] failed to show any significant clinical difference between the two drugs when used in equianalgesic doses. A major function of the hospice is research in and teaching about the correct use of analgesics; because of this it was decided to switch to morphine, which is more widely available — diamorphine being prohibited in many countries because of its supposed more addictive qualities. Pain in advanced cancer is the symptom which attracts most attention although others are common and perhaps just as distressing. A good example of the therapeutic approach to pain (and other symptoms) is the definition by Saunders [18] of pain as having physical, social, spiritual and emotional components. Patients are multi-symptomatic (Table I) so that polypharmacy is inevitable.

Drug control of symptoms is supplemented, where appropriate, by nerve block procedures, radiotherapy and chemotherapy (principally hormonal). All of these interventions take place in a therapeutic environment which stresses social, spiritual and psychological care; the impact of the ambience, adequate staffing, individual attention, and good staff-patient relationships should not be underestimated. Advocacy of oral morphine in this context is not meant to denigrate the use of e.g., methadone, but to report a unique body of clinical experience, supplemented by some scientific data. Many of the lessons learned have implications for the use of other major opiates and wide relevance to general therapeutics and clinical pharmacology.

Practical use

Pain management is based on the approach first suggested by Saunders 2 decades ago [16]. Morphine is given every 4 h in aqueous solution of single or double strength chloroform water; 5–180 mg/10 ml. Dosage is individualized by titrating dosage against the pain, increasing in a stepwise fashion until the patient is pain-free. The dose range employed is 2.5–180.0 mg of morphine sulphate every 4 h;
TABLE II
ORAL MORPHINE: ADJUVANT DRUGS
Adjuvant drugs prescribed for control of pain and other symptoms amongst patients receiving oral morphine. St. Christopher's Hospice Annual Statistics 1979, N = 474.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives</td>
<td>378</td>
<td>79</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>304</td>
<td>64</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>114</td>
<td>24</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>101</td>
<td>21</td>
</tr>
</tbody>
</table>

conventional dose increments are: 2.5, 5.0, 10.0, 15.0, 20.0, 30.0, 45.0, 60.0, 120.0, and 180.0 mg. Five doses per 24 h are usual (05.00, 09.00, 13.00, 17.00, 21.00 h) with a sixth dose at 1.00 a.m. if the patient is awake and in pain, or waking in pain in the mornings. Aqueous formulations are in general well absorbed so that bioavailability is likely to be satisfactory. The aqueous formulation has also a number of other advantages; it is easy for patients to swallow, has an acceptable taste with flexibility of dosage and high analgesic efficacy; there is too the ability to change the dose without the patient’s knowledge if this should be necessary. Prochlorperazine syrup (5.0 mg) is usually given in the same cup along with the morphine. This has the benefit of further improving the taste although a minority of patients find syrups sickly. Some discontinue the prochlorperazine once the patient has been having oral morphine for a few days or do not use it at all unless specifically indicated e.g., for emesis or agitation. An important feature of morphine usage is flexible prescribing e.g., 30/45 mg every 4 h. This allows nursing staff to alter dosage without delay or reference to a physician whenever it is needed because of a change in the pain pattern; this builds up confidence and patient-nurse relationships. The use of oral morphine is not a panacea and should be seen in the context of a therapeutic milieu and extensive use of adjuvant drugs (Table II). The frequency of increments depends on the patient’s level of pain, psychological status, previous therapy and presence of side effects. Many patients with advanced cancer can be adequately managed with

TABLE III
EQUIANALGESIC (TOTAL EFFECT) DOSES OF MAJOR OPIATES
Modified from Houde [7].

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>60 *</td>
<td>10</td>
</tr>
<tr>
<td>Heroin</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Phenazocine</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

* This figure is based on clinical analgesic efficacy studies. In clinical practice during repeated administration, morphine oral/intramuscular dosage ratio is 2–3 : 1, not 6 : 1.
minor opiates for long periods of time but the majority ultimately require oral
morphine. The point at which they should be transferred to morphine or another
major opiate depends on their response to other analgesics; the dose of morphine at
which they should start depends on the opiate used before (Table III). It is
important to be aware of the differences in milligram potency and the equianalgesic
dosages (both oral and intramuscular) of the common opiates when transferring a
patient from one drug and/or route of administration to another. Such data should
be treated with some caution in management of chronic pain as much is based on
acute clinical efficacy studies, for practical purposes however they are an adequate
guideline. In the regime described, no specific allowance is made for pharmaco-
kinetic (e.g., jaundice) or pharmacodynamic (e.g., severe respiratory disease)
abnormalities; dosage is individualized in exactly the same way as for persons who
do not present these problems.

Analgesic efficacy

Clinical experience suggests that oral morphine during repeated administration
has an analgesic efficacy compared to parenteral morphine in a ratio of 1:3 (i.e., 10
mg parenterally is equivalent to 30 mg orally) [6]. This is in conflict with data from
clinical analgesic studies which suggest a ratio of 1:6 [8] and reflects the known
improved analgesic efficacy of oral morphine in multiple doses [12] as compared to
single dose’[1] administration. Saunders [17] reported that (based on clinical assess-
ment) only in 2% of patients with pain due to advanced cancer was there difficulty
in achieving pain control with this approach. It should be pointed out that in this
context there is a distinction between ‘pain-free’ and ‘pain-controlled.’ Mount [14]
confirms that 85–90% of patients with advanced cancer tolerate oral morphine and
up to 95% get ‘excellent pain control with this basic approach in conjunction with
adjuvant therapy.’ This is true whether a traditional ‘Brompton Cocktail’ or a
modern simplified mixture without cocaine or alcohol are employed. In a controlled
study of oral morphine mixtures 8 (9%) of the 90 patients entered in the study [12]
could not be controlled using oral morphine as described above. A relevant feature
in these reports is the observation that oral morphine is an effective analgesic in all
hospital settings, but significantly more so in a palliative care unit emphasizing the
importance of psychological and other influences on pain relief. These reports
contrast with that of Beecher et al. [1] who found that oral morphine was little better
than placebo. This study, and the low relative bioavailability of oral morphine has
been the basis of much criticism of the use of morphine orally such that it does not
appear in some standard therapeutic texts although in fact Beecher et al.’s study did
not examine the efficacy of oral morphine when given repeatedly.

Morphine pharmacokinetics

Little is known of the pharmacokinetics of the aqueous formulation of oral
morphine. A crucial factor in the interpretation of available data is an appreciation
of the limitations of the analytical techniques employed and of the way in which oral morphine is used therapeutically, i.e., in individualized dosage given repeatedly. The most favoured analytical technique has been radioimmunoassay. Cross-reactivity between the antibody employed, morphine, and morphine metabolites (morphine-3-glucuronide, codeine, normorphine) is known to occur. In the case of the glucuronide after single doses of oral morphine it appears rapidly and in large excess because of presystemic ('first-pass effect') clearance by the liver and intestine. Even a relatively small element of cross-reactivity will give falsely elevated apparent plasma morphine levels. During chronic administration of morphine, the proportions of metabolites may change [22] and indeed increase. The majority of the kinetic work conducted on morphine so far has been on single dose profiles.

These studies (and other similar ones of clinical efficacy) are of doubtful relevance to advanced cancer patients with multisystem disease, receiving opiates repeatedly. The pharmacokinetic study most commonly quoted [3] showed 30% relative bioavailability of oral morphine. This followed single dose oral administration (tablet formulation) and showed low levels of plasma free morphine, high plasma and urine conjugated morphine levels and an apparent increased tendency to normorphine formation after oral administration. These data have been interpreted as explaining the poor analgesic efficacy of oral morphine in clinical studies such as that of Beecher et al. [1]. Recent work using radioimmunoassay has shown that when a suitable extraction procedure is employed [5] the apparent mean morphine plasma levels measured are about 30% lower than those revealed by methods without this procedure confirming that a significant error in apparent plasma levels is produced by cross-reacting metabolites. Amongst 23 advanced cancer patients the apparent 'trough' concentrations of morphine in plasma were pre-extraction 80 ng/ml (95% CI, 64–96 ng/ml) and post-extraction 26 ng/ml (95% CI, 20–33 ng/ml) — both calculated to 10 mg morphine base. These values are higher than would be predicted from data available from single dose morphine pharmacokinetic studies and confirm that repeated oral morphine administration is an effective method of drug delivery. Recent pharmacokinetic data [19] confirm that dosage of aqueous morphine must be individualized because of between-individual variations in metabolism (Table IV). Definition of changes in morphine metabolism during chronic repeated administration awaits the result of further studies.

| TABLE IV  |
| MORPHINE KINETICS IN CANCER |
| Adapted from Sawe et al. [19]. |
| Oral bioavailability: 15–64% |
| Terminal half-life: 58–467 min |
| Vd: 0.95–3.75 l/kg |
| Serum clearance: 5.0–16.1 ml/min/kg |
Common unwanted effects of morphine

(1) Constipation

The commonest side effect of morphine is constipation and this must be anticipated with regular laxatives administered once opiate therapy begins and a check kept on bowel habit.

(2) Sedation

Sedation is usually a transient problem when morphine is begun and as long as dosage is not increased too rapidly, often clears in a few days. Sometimes it persists and a balance needs to be struck between the level of the pain and the degree of sedation. Patients often find sedation intolerable and prefer a minor level of pain which does not ‘bother’ them to a clouded sensorium.

(3) Nausea and vomiting

Nausea and vomiting appear to be less of a problem in those confined to bed and a greater problem in women [21] although the reasons for this are unclear. Sometimes, it is severe and necessitates use of combinations of antiemetics, parenteral medication (see below) or responds to the substitution of phenazocine or another major opiate for morphine. It is important to remember that there are many reasons why patients with advanced cancer given opiates might vomit in addition to the opiate itself.

Tolerance and dependence

These issues are linked in many people’s minds and will be dealt with together. Tolerance in the context of patients dying from cancer has implied that once morphine or other major opiates are administered, a progressive and relentless increase in dosage is required to obtain the same or even a diminished therapeutic effect. This is not true. When oral opiates are used in the fashion described some increase in dosage with time does occur, but does so in the context of progressive disease, is moderate in magnitude (e.g., 30% increase with 6 weeks’ continuous use) and within manageable limits. There is no doubt that gross tolerance to opiates by whatever route of administration they are given can be demonstrated in pharmacological studies in animals and man, but the models used for these studies have often been inappropriate [4] to cancer patients; subjects were not in pain, dying from incurable disease and having oral opiates administered repeatedly in individualized dosage. Dosage has often been empirically determined and changed according to artificial criteria and not in response to clinical necessity. It is clear from the histogram (Fig. 1) that 70% of patients never receive more than 20 mg of oral morphine every 4 h irrespective of the duration of use as the majority are managed satisfactorily on one of the lower doses. Some element of pharmacological tolerance occurs during therapeutic use as it does to many other drugs but whilst pharmacologically interesting, it is not often therapeutically important and should not prevent
Fig. 1. Maximum individual doses of oral morphine prescribed for St. Christopher’s Hospice inpatients during 1979. Reproduced by kind permission of the New England Journal of Medicine.

the use of opiates when indicated. Similarly, dependence has often been examined in models and contexts irrelevant to terminally ill patients with chronic pain. Drug seeking behaviour is not a problem in this population provided adequate doses of analgesics are used; it is appropriate behaviour for persons dying from cancer and in chronic pain to seek relief, and to label such people as addicts because of this is foolish. This problem is most likely to arise in chronic pain when major opiates are not administered in accordance with their pharmacological characteristics, e.g., intermittently, or ‘as required.’ Ignorance on the part of nursing and medical personnel about the correct use of opiates in this context is thus likely to create self-fulfilling prophecies concerning ‘addiction.’ Patients receiving opiates repeatedly are undoubtedly physically dependent (i.e., a withdrawal syndrome will follow abrupt withdrawal of the opiate). Anecdotal reports (when this has occurred in error) indicate that the withdrawal symptoms from oral opiates are mild. At a practical therapeutic level, physical dependence is not a problem as opiates may be withdrawn completely (if appropriate) or the dosage reduced, provided this is done in a stepwise gradual fashion (similar to established practice for corticosteroid withdrawal). Tolerance and dependence and misunderstandings about their relevance to chronic cancer pain are major contributory factors to the poor management
of pain in cancer patients [11]. These misunderstandings obviously do not apply only to morphine, but to the use of other opiates as well.

**Respiratory depression**

Clinically, this is not a problem when morphine is used in the way described even though many patients with advanced cancer have primary or secondary respiratory tract disease, and are simultaneously receiving other depressant drugs in addition to morphine. Mount [14] reported that in treating several hundred patients with oral opiates over a 5.5 year period opiate antagonists had only to be given on three occasions because of respiratory depression. Examination of the literature on the effects of opiates on respiratory function reveals that in clinical studies the drugs have been administered parenterally in standard dosage, usually to postoperative surgical patients. The elevations in pCO₂ produced (or reduction in sensitivity to CO₂ using rebreathing techniques) have been modest in degree and often clinically insignificant [15]. These results are not necessarily applicable to the situation where morphine is given orally, in individualized dosage to medical patients. Parenteral administration of opiates produces higher peak and more rapid changes in plasma levels and these are likely to be responsible for increased and more serious side effects including ventilatory failure.

A recent study [23] of 20 patients with advanced cancer reveals no evidence that chronic ventilatory failure is either common or severe in patients receiving high doses of oral morphine (> 100 mg/24 h) as judged by arterial blood gases and simple clinical measures of respiratory function. All patients were pain-free at the time of examination and had significant levels of morphine in their plasma. The presence of pain is itself an antagonist to respiratory depression, and an individualized, gradual approach to changes in dosage and in the morphine plasma levels consequent on the oral route of administration perhaps allows pharmacological tolerance to the respiratory depressant effect of morphine to develop whilst still allowing pain to be relieved.

**Slow-release morphine**

A new slow-release (MST continu; Napp Pharmaceuticals Ltd.) formulation of morphine (Fig. 2) is available in Great Britain and produces prolonged plasma morphine levels [10]. This is not the same as prolonged analgesia and it has not yet been exposed to controlled clinical trial in chronic pain from advanced cancer. Data on cancer patients at steady state [5] suggest that there is little relationship between morphine plasma level and the presence/absence of analgesia. The preparation however seems effective and convenient and is invaluable for domiciliary care; it may also prove to be associated with fewer side effects such as nausea and vomiting than aqueous morphine formulations because of slower changes and lower peaks in morphine plasma levels.
Fig. 2. Plasma morphine levels in 3 healthy volunteers after dosage with 10 mg controlled release morphine sulphate at 0, 12 and 24 h. Reproduced by kind permission of Leslie et al. [10].

**Brompton cocktail**

The use of oral morphine (or diamorphine) in Great Britain is based on traditional strong analgesic mixtures e.g., ‘Brompton cocktail’ (morphine, cocaine, alcohol, syrup and chloroform water), which have been in use for many years. A wide variety of analgesic mixtures were used, the precise formulation varying from one hospital pharmacy to another, but have become popularly known by the name of the Brompton Chest Hospital, London. Hospice units used the mixtures for their patients but it was not until the last decade that scientific evaluation [13] of the ‘Brompton cocktail’ and its constituents resulted in a simplified analgesic mixture. The routine inclusion of alcohol has been discontinued; cocaine has not been shown to confer benefit, and has also been dropped. Alcohol in small amounts or chloroform water are necessary as bacteriostatic/fungicidal agents [14] to prolong shelf-life (about 1 month after opening for morphine in chloroform water). Morphine or diamorphine made up in water alone are very bitter and chloroform water also improves the taste. A controlled study comparing a ‘Brompton mixture’ (morphine, cocaine, ethyl alcohol, syrup and chloroform water) to a morphine solution (morphine, syrup, essence of orange flavouring) showed that side effects such as confusion, nausea and drowsiness were equally common with both formulations [13]. A phenothiazine may be added to the mixtures as an antiemetic although
routine inclusion is probably unnecessary once morphine initiation is complete. An open pilot study suggests (Walsh, unpublished observations) that when prochlorperazine is used with oral morphine, the sedative and coanalgesic actions are as important as any antiemetic one. Chlorpromazine or methotrimeprazine are favoured alternatives to prochlorperazine. Further evaluation of the role of phenothiazines used in conjunction with morphine are in progress.

Role of diamorphine (heroin)

Many units use oral diamorphine dispensed and prescribed in a similar fashion to that already described for morphine. Diamorphine is useful too when a parenteral opiate is needed because a smaller volume of injection is required than for morphine at equivalent dosage. This is of obvious value in emaciated persons where repeated intramuscular injections are undesirable; a number of other drugs may be equally satisfactory e.g., hydromorphone. About 15% of admission to St. Christopher's Hospice require maintenance treatment with parenteral diamorphine due to inability to take oral medication or in a small number to poor response to oral morphine. In the latter situation the use of parenteral opiates seems to confer improved analgesic benefit. Younger patients ( < 65 years, particularly females) appear to require higher doses of both oral and parenteral opiates. This may be due to gender differences in pharmacokinetics, different primary site incidence/disease pattern or perhaps better interpersonal identification between nursing staff and females in similar age groups [2]. Controlled studies conducted in patients with advanced cancer receiving maintenance oral morphine or diamorphine and in cancer patients postoperatively show no substantive therapeutic difference between morphine and diamorphine when differences in milligram potency [9] are taken into account. During repeated administration, oral heroin 5 mg appears to be equianalgesic to morphine 7.5 mg and intramuscularly heroin 5 mg to morphine 10 mg. The separate issue of whether diamorphine is more addictive than morphine is not very relevant to persons in chronic pain dying from cancer.

References