Pain control in terminal disease

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Summary

Pain control is recognised as perhaps the most important single objective in the patient with terminal disease. Cancer, cardiovascular disease and obstructive airways disease are foremost among many causes of pain requiring control in the terminal phase. Spiritual, emotional, religious and socio-economic factors are important in raising or lowering the pain threshold.

Analgesic strategies include use of drugs, neurosurgery, radiotherapy and supportive measures which may be brought to bear singly or in combination as required. Pain is clinically classified as being acute or chronic, by the type of patient, and by a series of common pain syndromes and their pathological mechanisms.

General concepts of control of pain and discomfort in disease are discussed, together with a brief comment on epidemiology, in the first part of the article. Rationale is then discussed under the following headings: (i) principles of pain control; (ii) causes of pain; and (iii) analgesic modalities and factors impinging on their efficacy.

Patients with cancer-related pain account for a large proportion of the terminally ill. They usually require pain control as a major component of therapy.

Mortality data reveal that the incidence of cancer as a terminal illness is significantly higher in First-World countries than in the Third World (figures from various countries are shown in Table I). There is therefore a bias towards cancer in discussions of pain control in terminal illness.

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<th>TABLE I. DEATHS FROM CANCER (% OF TOTAL DEATHS PER ANNUM)</th>
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<td>USA</td>
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<td>The Netherlands</td>
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Pain has been defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (International Association for the Study of Pain).2 Perhaps one of the most important therapeutic aspects of terminal care is adequate and if possible complete pain control. Because pain is subjective, the physician is limited in his assessment and must always believe the patient.

Pain can be: (i) acute, well defined and related to a very definite temporal pattern, and characterised by subjective and objective signs (for example hyperreactivity of the autonomic nervous system), which allows substantiation of the patient's complaint and some objective assessment thereof; or (ii) chronic, persisting for longer than 6 months (e.g. cancer), and characterised by a lack of objective signs and by marked changes in the patient's personality, lifestyle and functional ability — it is important, however, for treatment to be aimed at the cause and also at the factors which predispose to the psychological breakdown and social instability of the patient and family.

Pain in cancer patients can be subdivided as follows:

1. By the type of patient: (i) cancer-related pain, (a) associated with the diagnosis of cancer, and/or (b) with cancer therapy (surgery, chemotherapy or radiotherapy); (ii) chronic cancer-related pain, (a) associated with cancer progression, and/or (b) with cancer therapy (surgery, chemotherapy or radiotherapy); (iii) pre-existing chronic pain and cancer-related pain; (iv) a history of drug addiction and cancer-related pain, patients being (a) actively involved in illicit drug use, (b) in methadone maintenance programmes, and/or (c) with a history of drug abuse; and (v) cancer-related pain in the dying patient.

2. By a series of common pain syndromes3 and their pathological mechanisms: (a) pain associated with direct tumour involvement (at the Sloan Kettering Institute in the USA3 78% of all pain problems in inpatients and 62% of those in outpatients fell into this category — these problems related to metastatic bone disease, nerve compression or infiltration, or hollow viscus organ involvement and were by far the most common causes of pain in cancer patients); (ii) pain associated with cancer therapy (surgery, chemotherapy or radiation therapy) (at the Sloan Kettering Institute3 19% of pain problems in inpatients and in 25% of those in outpatients fell into this category); and (iii) pain unrelated to cancer or its therapy (at the Sloan Kettering Institute3 this accounted for 3% of pain problems in inpatients and 10% of those in outpatients).

In essence the object of pain control would be to obliterat all unpleasant sensation while allowing the patient unimpeded psychic function. A central factor motivating development of standardised and reproducibly effective hospice care was the appalling mental and physical state of terminally ill patients,1,8 particularly those with intractable pain. Incessant and intractable pain8 (Richard Lammerton, St Joseph's Hospital, London — personal communication, 1980) precludes the application of any therapeutic or supportive regimen which requires communication with and participation by the patient and ensures a tortured and undignified passage to death.8

In pursuit of the ideal of comfort and freedom from pain, one must constantly be aware of the possibility of inadvertently applying 'euthanasia' with the modern drugs at our disposal — this may even be a conscious and positive urge.

Epidemiology

The following points are useful: (i) the prevalence of pain increases with the progression of the disease; (ii) causes of pain are often multiple; (iii) approximately 15% of patients with non-metastatic disease have pain; (iv) approximately one-third of patients with metastatic disease report that pain:...
with their lifestyle and needs urgent attention; (e) between 60% and 90% of patients with advanced disease have substantial pain; and (vi) about 25% of all cancer patients are without pain relief.

Rationale of pain control

Principles

The following important principles should be meticulously applied: (i) taking a history of the patient; (ii) evaluation of the psychological status of the patient; (iii) careful medical and neurological examination; (iv) continual reassessment of the patient; (v) response to and ongoing care for patient and family from diagnosis through the terminal event and beyond (bereavement); (vi) provision of total analgesia without cripping side-effects such as gastric irritation with nausea and vomiting; (vii) avoidance, as a side-effect, of central nervous system depression resulting in diminished consciousness and mental function; and (viii) anticipation of and appropriate attention to constipation, which is unfortunately a common and unpleasant side-effect of analgesics.

Dosage of analgesics

1. Drugs should be of appropriate potency and used in the dosage required, no more and no less. The only determinant must be the intensity of the pain and the degree of incapacity suffered by the patient — it must always be assessed in the final analysis with reference to the underlying disease.

2. Dosage should also be related to renal function and the frequency of drug administration, with regulation appropriate to the serum half-life. The available analgesics are usually used 4-hourly. The most important principle as regards administration is that it should never be ‘as necessary’ but always on a formal regular dosage schedule.

Factors lowering the pain threshold

Factors lowering the pain threshold1,4 (Lammerton - personal communication) include isolation of the patient, who tends to withdraw from his environment. There are also potent external factors at work within the immediate family which will contribute to the patient’s total isolation.

Fears, fantasies and anxiety will also operate. These are influenced by social factors, spiritual factors, and mental factors which will affect the content and expression of these thought processes. Depression is inevitable, and physical factors such as intractable nausea and vomiting make things worse. Pure physical revulsion and discomfort arise from such things as necrotic and discharging lesions and excreta-soiled bedclothes. Incontinence, dyspnoea and insomnia are also potent factors and must be dealt with as they are recognised.

Without resolution of the abovementioned problems, acceptable analgesia may be extremely difficult to achieve. Identification and diagnosis of these factors may be difficult, requiring time, patience and all one’s acumen and expertise. Even then it is often necessary to draw upon resources of the hospice team in elucidation and solution of these problems.

Supportive care

Supportive care6,7,8 centres around the education of the family, other health care professionals and the proper use of analgesics. All the other activities of the hospice team are integrated to provide the supportive care which must accompany the other treatment modalities.6,7 Because it is so apt, concise and accurate I should like to quote directly from Foley’s article1 on the treatment of cancer pain: ‘Pain is one of the most feared consequences of cancer. Changing attitudes towards the effective use of narcotic analgesics, the development of novel routes and methods of administration, a clinical approach based on scientific principles and humane care offer the promise of improved management of pain in patients with cancer.’ These remarks are equally applicable to all terminally ill patients who have pain and discomfort.

Behavioural techniques

Behavioural techniques,3,7 including relaxation training, biofeedback and cognitive and behavioural training, hypnosis and music therapy, have all been integrated into the management of cancer pain with encouraging results.

Causes of pain in terminal illness

Terminal or hospice care is not a new discipline and the basic principles of diagnosis and treatment are the same as in other surgical or medical disciplines. Hence the need to make: (i) an anatomical diagnosis; and (ii) a pathological diagnosis, both of which are mandatory before a totally effective analgesic strategy can be designed and implemented. It must be remembered that the objective is always palliative and supportive, never curative.

Pain impulses are conducted from the peripheral nerve endings to the central nervous system via two different types of fibres, slow (autonomic) and fast (somatic). The impulses and sensations from slow conductive fibres are nonspecific in character and arise from deep-seated structures and organ parenchyma. For example, oesophageal lesions cause characteristic pain seen as dysphagia; the pain is sometimes perceived after the stimulus has occurred, becomes progressively worse, subsides slowly and is poorly localised. The fast pathway results in immediate perception of the impulse; pain is severe, appears almost simultaneously with application of the pain stimulus (for example in pleuritic or peritoneal pain) and is accurately localised.

Disease processes in general, and disseminated carcinomatosis in particular, can affect any structure of the body, but only some produce pain. For example, in carcinoma of the colon no pain is felt until the lesion becomes obstructive. Hepatic pain may be felt only when metastases and/or the disease process affect the capsule and stimulate the nerve endings there.

Anatomical diagnosis

Pain can be elicited very specifically in different areas of the body. For example, bone pain can arise from the periosteum, the bone itself, or the synovial membrane in joints and around tendon sheaths. Serous surface pain may be pleural, peritoneal, pericardial or meningeal. Muscular pain can be caused by smooth muscle (characteristic colic in the gastro-intestinal and renal tracts) or striated muscle (elicited through contractures and spasm of the muscle, causing characteristic cramps). When organs are affected pain is elicited from the skin, lungs, liver, spleen and central nervous system, where it may be characteristic if nerve roots are affected by the disease process. The sensation is usually nonspecific, poorly localised and perceived through slow conduction. Enlargement of the liver and spleen and malfunction of the lungs can be mechanisms of pain production and distress (dyspnoea).

Pathological diagnosis

A variety of diseases can be responsible for terminal disease and therefore responsible for pain. These include: (i) neoplastic
**Analgesic modalities and factors influencing their efficacy**

To quote from Goodman and Gilman: "Any meaningful discussion of the action of analgesic agents must include some distinction between pain as a specific sensation, subserved by distinct neurophysiological structures, and pain as a suffering (the original sensation plus the reactions evoked by the sensation). There is general agreement that all types of painful experiences, whether produced with experimental techniques or occurring clinically as a result of pathology, include both the origin of sensation and the reaction to that sensation.

'The effects of analgesics on both experimentally produced and pathological pain have been carefully studied in man. The latter type of pain cannot be terminated at will, and the meaning of sensation and the distress it engenders are markedly affected by the individual's previous experiences and current expectations. In experimentally produced pain measurements of the effects of morphine on pain threshold have not always been consistent. Moderate doses of morphine are effective in relieving clinical pain and increasing the capacity to tolerate experimentally induced pain. Opioids obtund the response to painful stimuli at several loci in the brain. Not only is the sensation of pain altered by opioid analgesics, but the effective response is changed. This latter effect is best assessed by asking patients about the degree of relief produced by the opioid. A patient's ability to tolerate the pain may be markedly increased even when the capacity to perceive the sensation is relatively unaltered.'

Analgesics must be prescribed rationally and continuously, on the basis of the drug's serum half-life and the patient's renal function. Morphine and paracetamol should both be used 4-hourly.

**Mild analgesics**

Mild analgesics are almost always orally administered. *Aetysalicylic acid* (disprin or aspirin), 300 - 600 mg (1 - 2 tablets) is given 4-hourly. Remember its tendency to support a bleeding diathesis (anti-platelet coagulation factor), act as a trigger factor for bronchospasm in asthmatics and/or patients with chronic obstructive airway disease, and caused gastric irritation. Oral mild analgesia with aspirin has the advantage of low toxicity and has a respiratory stimulant effect, and patients do not develop tolerance or addiction.

*Codeine* (methylmorphine), in doses of 10 - 30 mg 4-hourly, is an excellent analgesic. There is, however, a first-pass hepatic effect, and 10% of the dose is demethylated in the liver to form morphine. Codeine causes constipation, depresses respiration, and can also cause nausea and vomiting. Mental clouding and dysphoria together with a tendency towards increased pressure in the biliary tract are some other adverse effects. *Paracetamol* (acetaminophen) is a major metabolite of phenacetin; it is also antipyretic but can be both nephrotoxic and hepatotoxic (it also induces microsomal hepatic enzymes). Toxicity is low, however, and paracetamol acts synergistically with codeine. There are many effective preparations to choose from, but renal toxicity will increase in direct proportion to the number of substances combined in an analgesic tablet over and above the paracetamol and codeine combination. Another mild analgesic is *mefenamic acid.*

**Moderately potent analgesics**

Examples are dipipanone plus cyclizine (Wellconal), tildine (Valoron) and nefopam (Acupan), which are nonspecific. When used in higher doses (Table II) they become powerful analgesics.

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<th>TABLE II. DOSE-RELATED INTENSITY OF ACTION</th>
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<td>Moderately potent</td>
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<td><strong>Wellconal</strong></td>
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<td><strong>Valoron</strong></td>
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<td><strong>Acupan</strong></td>
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**Powerful analgesics**

Examples are morphine, pethidine, papaveretum, morphine tartrate plus cyclizine tartrate, and cannabis (successfully used in certain hospice units). The following analgesics are currently available in the RSA (they are not listed in order of potency or pharmacological grouping):

*Cyclimorph* contains morphine tartrate either 10 or 15 mg and cyclizine tartrate 50 mg. It is given 4-hourly by intramuscular or intravenous injection.

*DF. 118* contains dihydrocodeine tartrate. It is given orally (30 mg tablets) or by intramuscular or subcutaneous injection (50 mg/ml) 4-hourly.

*MST Continus* contains morphine sulphate in a controlled-release matrix and comes in 10 mg and 30 mg tablets, providing a twice-daily dosage.

*Numperon* (oxymorphone 1,5 mg/ml) is given by intramuscular or subcutaneous injection 4-hourly.

*Omnopon* (papaveretum 20 mg/ml) is given by intravenous or intramuscular injection 4-hourly.
Pharmacological adjuncts

These include: (i) prostaglandin synthetase inhibitors, a group of non-steroidal anti-inflammatory drugs very important in the treatment of bone pain from secondary metastases; (ii) antidepressants; (iii) phenothiazines, which may be neuroleptic, sedative, anti-emetic or antihistaminic; (iv) cyclizine (Valoid), an anti-emetic of an unrelated group; and (v) benzodiazepines, which may be hypnotics, tranquillisers, sedatives or anti-depressants.

Pharmacological agents used locally for pain control

These are used: (i) to anaesthetise the peripheral nerve — any potent local anaesthetic can be used; (ii) to destroy a nerve route with neurolytic agents; (iii) to anaesthetise via the epidural route, once again with any efficacious anaesthetic, or intrathecally, when opiates can be used; (iv) to anaesthetise intraventricularly, once again with opiates, in order to achieve an action on the brainstem; and (v) to perform chemical hypophysectomy with an obliterator substance.

Early treatment of local pain before the development of serious nerve injury and consequent deafferentation is important. All the above techniques require special skills and are therefore not always available.

Important principles

The same basic important principles apply as much to the drug therapy of terminally ill patients as they do to drug treatment in any other discipline: (i) use a medicine appropriate to the patient's needs, for example mild analgesia for mild pain; (ii) be familiar with the side-effects of the preparation selected and any special precautions — opiates, for example, depress respiration, cause constipation and are epileptogenic; (iii) be familiar with the pharmacokinetics of the drug you are using — details such as serum half-life and routes of excretion are vital to correct dosage, and dosages of drugs excreted via the kidney are adjusted according to the creatinine clearance; (iv) choose two or three drugs from each category of potency, and become thoroughly familiar with them and all their characteristics; (v) enhance the analgesic effect by the addition of any of the other modalities mentioned above — use discretion, however, since inappropriate application could compound the issue; (vi) transfer from one category of potency to another, either by changing the drug used, for example from aspirin to morphine, or by varying the dose of the same compound — for example, codeine can be used as a mild analgesic but with increased dosage becomes one of moderate potency.

Conclusion

Pain is one of the most feared consequences of terminal disease, particularly cancer. Changing attitudes towards the effective use of narcotic analgesics, the development of new routes and methods of administration, and a clinical approach based on scientific principles and humane care offer the promise of improved management of pain in terminally ill patients. The philosophy of pain control in terminal illness is reproducibly effective whether applied to pain and discomfort from cancer or other causes. I have attempted to provide a very broad overview, highlighting the principles and concepts in the management of pain in terminally ill patients and also, where appropriate, listing some practical guidelines for the diagnosis of pain, factors which may lower the pain threshold, and the various modalities available for the relief of pain.

REFERENCES


Pethidine hydrochloride (50 mg/ml) is given by intramuscular or intravenous injection (50 - 100 mg 4-hourly). It can lower the blood pressure precipitously. Physepine contains methadone hydrochloride 10 mg/ml and is given by intramuscular or subcutaneous injection (5 -10 mg 4-hourly).

Sosegon (pentazocine) is given 4-hourly by intramuscular injection (30 mg/ml) or orally (½ - 2 x 50 mg tablets). Temgesic (buprenorphine) is available in 0,3 and 0,6 mg ampoules and is given by intramuscular injection 6 - 8-hourly.

The reader is advised to consult any pharmacological text for full pharmacological and pharmacokinetic details of these drugs.