Use of the Brompton mixture in treating the chronic pain of malignant disease

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Physical, psychological, financial, interpersonal and spiritual factors all modify the appreciation of chronic pain. The Brompton mixture is a highly effective, flexible, safe and convenient means of controlling the chronic pain of malignant disease. The mixture is a solution containing morphine; the dose of narcotic can be varied with the need for analgesia. It is given regularly, usually every 4 hours, with a phenothiazine, the main aims of therapy being prevention of pain rather than treatment, an unclouded sensorium and a normal affect.

L'appréciation de la douleur chronique est modifiée, à la fois, par des facteurs physiques, psychologiques, financiers, sociaux et spirituels. La mixture Brompton offre un moyen grandement efficace, souple, sûr et pratique de contrôler la douleur chronique associée aux maladies malignes. La mixture est une solution contenant de la morphine; la dose de ce narcotique peut varier selon les besoins d'analgésie. Elle est administrée à tous les 4 heures, en association avec une phénothiazine. Les objectifs principaux de ce traitement sont de prévenir la douleur plutôt que de la traiter, d'émousser les sens et de maintenir un affect normal.

The nature of chronic pain

It is in treating acute pain that most physicians gain experience in the use of analgesics. Acute pain is reversible. It warns us of a problem that needs attention. It can therefore be viewed as linear, with a beginning and an end. Chronic pain, however, can be characterized as a vicious circle with no set time limit. The fearful anticipation of its perpetuation leads to anxiety, depression and insomnia, which in turn accentuate the physical component of the pain.[1] Leshan[2] suggests that meaninglessness, helplessness and hopelessness are characteristic of the unreal nightmare world in which the patient with chronic pain lives every day. Saunders[3] has coined the term "total pain" to describe the all-consuming nature of chronic pain and our need to attack all of its components — physical, psychological, financial, interpersonal and spiritual. For the patient with advanced malignant disease, pain forcibly reminds him of his prognosis and thus further accentuates his total agony.

Aims of treatment

The aims of treatment of the intractable pain of advanced malignant disease include the following:

1. *Identifying the cause:* Clarification of the cause is an essential first step in symptom control and may often lead to specific forms of therapy (e.g., radiotherapy for a localized bony metastasis, estrogens in carcinoma of the prostate, or purgatives in pain due to constipation).

2. *Preventing pain:* The aim is to anticipate and prevent pain rather than treat it. This requires the *regular* administration of appropriate amounts of analgesic. Waiting for pain to reappear (as with "p.r.n." orders) only accentuates the problem of pain control. "The physician should not wait until the pain becomes agonizing; no patient should ever wish for death because of his physician's reluctance to use adequate amounts of potent narcotics".[4]

3. *Erasing pain memory:* As the anxious anticipation and memory of pain is lessened by successful pain prevention, the amount of analgesic required will frequently decrease.

4. *An unclouded sensorium:* Many patients feel trapped between perpetual pain on the one hand and perpetual somnolence on the other. The balance, a pain-free state without sedation, requires careful individual regulation of analgesic dose according to the patient's needs.

5. *Normal affect:* The ability of a patient to relate to his environment with a normal affect, neither euphoric nor depressed, is an obvious treatment aim.

6. *Ease of administration:* Oral administration of analgesics can allow a patient to retain a degree of independence and mobility that he cannot have when analgesics are given parenterally. Cachexia may also make regular parenteral medication difficult and painful.

Use of narcotics

The current North American anxiety surrounding the use of narcotics for the intractable pain of advanced malignant disease is summarized in the following points: "Giving narcotics is bad management. Narcotics give you 'ups and downs' producing addiction and destroying the personality. They depress cortical function."[5]

Our experience suggests that with attention to detail, none of these statements need be true, and that all of the treatment aims outlined may be achieved, with few exceptions.

With moderate to severe chronic pain, only the narcotic analgesics provide adequate control. Milder analgesics should always be tried for less severe pain and may be helpful in combination with more potent drugs. A wide variety of agents is available; Catalano[6] presents a good recent review.

The Brompton mixture

In our experience the Brompton mixture is effective in most cases of severe pain and as a liquid has advantages over tablets for oral administration:

1. The dosage can be easily adjusted to meet the patient's need.

2. Many patients have dysphagia, either functional or due to local disease, and find a syrup easier to swallow than a tablet.

The Brompton mixture is used when non-narcotic and milder narcotic preparations are ineffective. Lengthy anticipated survival is *not* a contraindication because, with care in adjusting the dosage to meet the patient's need, the mixture may be used for periods of many months to several years without dose escalation.

Although generations of British physicians have gained familiarity with variants of the oral narcotic mixture bearing the name of the Brompton Chest Hospital, it was not until 1973 that this formulation was recognized in the "British Pharmaceutical Codex".[7] The important experience of Saunders and her coworkers[3,8] at St. Christopher's Hospice and St. Joseph's Hospice has led to a refinement and standardization of approach, which has been associated with greatly increased effectiveness in achieving the above aims of therapy.

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The standard mixture contains a variable amount of morphine, 10 mg of cocaine, 2.5 ml of ethyl alcohol (98%), 5 ml of flavouring syrup and a variable amount of chloroform water, for a total of 20 ml. The contributions to the effectiveness of this mixture of the small amount of cocaine and the stabilizing effect of the ethyl alcohol are uncertain. Further elucidation must await the results of trials aimed at simplifying the mixture.

For most patients the chronic pain of advanced malignant disease can be controlled with 5 to 20 mg of morphine per dose of the mixture, but small or elderly patients may require as little as 2.5 mg. The usual sequential doses of morphine given are 2.5, 5, 10, 15, 20, 30, 40, 60, 90 and 120 mg. This standard elixir is always given with a phenothiazine. The phenothiazines are potent antiemetics and are thus useful in countering vomiting, a frequent side effect of narcotics. Experience also suggests that they potentiate the narcotic analgesia. Prochlorperazine, 5 mg in 5 ml, is usually highly effective as an antiemetic, with little sedative effect. If restlessness or agitation is a feature, chlorpromazine, 10 to 25 mg, may be substituted. Twycross[9] has shown a shelf life of sustained effectiveness that exceeds 8 weeks.

Administration

In adjusting the dosage of narcotic and phenothiazine to achieve a pain-free state without sedation, a number of factors are important:

- The morphine elixir should be given in 20-ml doses with the phenothiazine every 4 hours around the clock because the serum half-life of morphine taken orally is about 4 hours. Occasionally a patient may require a 3-hourly schedule. The night-time dose is omitted only when the patient can sleep through the night free of pain. Careful attention to exact dosage and timing will pay dividends in results.
- For most patients a pain-free state can be achieved by giving sequential increments in narcotic dose.[10] To treat excruciating pain one may elect to start with a higher narcotic dose, then make sequential decrements until analgesia without sedation is achieved (Fig. 1). In determining the dosage required, dose alterations should be made at intervals of 48 to 72 hours. During this period further analgesia can be achieved with the use of supplemental analgesics as required.
- In general, it is wise to change only one variable, the narcotic or the phenothiazine, at a time. Since the phenothiazines and morphine are synergistic, great care must be exercised. Small changes in either variable may produce profound changes in analgesia and sedation.
- Initiation of narcotic therapy will usually produce transient sedation lasting 48 to 72 hours. It is important to reassure both patient and family that pain can and will be controlled and that the initial drowsiness is temporary. Their confidence that control can be achieved will promote analgesia.
- Dispensing the morphine mixture and the phenothiazine syrup separately allows greater flexibility in adjusting dosage. Once a continuous pain-free state is achieved, they may be combined in dispensing for greater ease of administration.
- Careful observation of the patient's condition over a complete 24-hour period may suggest augmentation of one or two specific doses at periods of peak activity.
- If parenteral medication becomes necessary, the equivalent dose of morphine is one half the previous oral dose. Thus, a patient whose pain has been controlled with 30 mg taken orally would then receive 15 mg intramuscularly.[8]
- The maximum effective oral dose of morphine is ill defined. Recent experience at St. Christopher's Hospice (C. Saunders: personal communication, 1975) suggests that continuing effectiveness may be obtained in some patients with oral doses of 90 mg or more; however, most patients' pain can be controlled with less than 30 mg *q4h*.

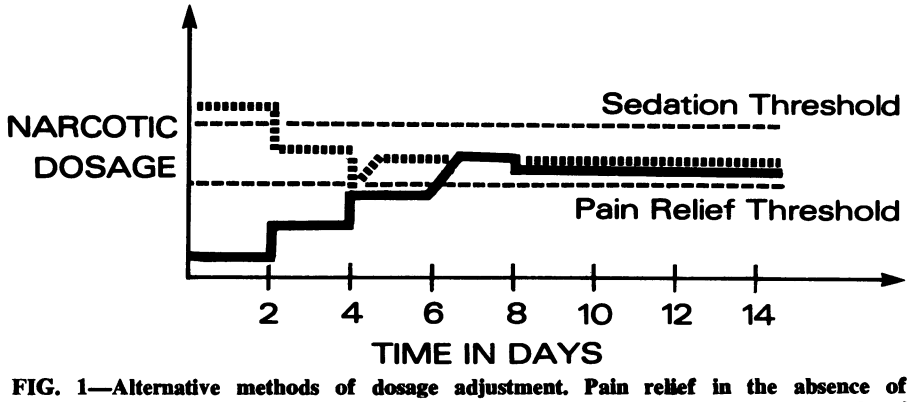

FIG. 1—Alternative methods of dosage adjustment. Pain relief in the absence of sedation may be achieved with sequential increments in narcotic dose at intervals of 2 days (▬▬). In a few cases the severity of the pain will require an initially high dose, followed by sequential decrements until the pain reappears (■ ■ ■ ■). A slight increase in dose provides analgesia without sedation (- - - -).

Adverse effects

These basically are the adverse effects common to all narcotics and include the following:

Sedation: When narcotic therapy is introduced transient sedation frequently occurs. The phenothiazine may exaggerate this effect. However, patients with advanced malignant disease often have other causes for somnolence (e.g., hepatic or renal insufficiency, or metastases).

Nausea and vomiting: Routine use of a phenothiazine with the mixture counters this common side effect of all narcotics. If a patient is vomiting before therapy is instituted, control should first be achieved with parenteral medication and subsequently maintained with oral medication.

Constipation: The combined effects of poor dietary intake, dehydration, inactivity and narcotic therapy almost invariably lead to constipation. This should be prevented by using a combination of a stool softener and a bowel stimulant (e.g., dioctyl sodium sulfosuccinate and senna concentrate).

Tolerance-dependence: Evans[11] and Twycross[8] both reported that dependence (addiction) is not a problem when narcotics are used for the pain of malignant disease. Marks and Sachar[12] stated: "the excessive and unrealistic concern about the danger of addiction in the hospitalized medical patient is a significant and potent force for undertreatment with narcotics". It would seem, rather, that undertreatment with analgesic medication may encourage craving and psychological dependence. Progressive tolerance and escalating dosage requirements are often given as reasons for delaying the onset of narcotic therapy. Our own experience confirms that of Twycross[8] that a change in dosage requirement heralds a change in disease status rather than tolerance.

Other adverse effects: Extrapyramidal effects, orthostatic hypotension and other side effects of the phenothiazines must be watched for but they occur infrequently with suggested doses. Because of phenothiazine's synergism with morphine, a small dose of the former is often sufficient. Although cocaine may be highly toxic to habitual abusers, there is some question whether tolerance to cocaine develops.[13] The dose of cocaine used by us is similar to that used at St. Christopher's Hospice and is one half the dose suggested in the "British Pharmaceutical Codex".[7] It has

not led to important toxicity. Hypersensitivity reactions to morphine and to the phenothiazines are rare. When used as outlined above, the Brompton mixture provides convenient and uniform pain control without important adverse effects.

Case reports

Three current cases illustrate the use of the Brompton mixture.

Case 1: A 70-year-old woman with breast carcinoma had received the Brompton mixture intermittently for more than 1 year at the time of this report (Fig. 2). It was initially instituted during radiation therapy for lower thoracic back pain due to spinal metastases. At that time she was bedridden and had a decubitus ulcer. Over the ensuing 40 weeks she was given progressively smaller doses of morphine in the mixture and felt well enough to walk short distances. Once she was pain-free the mixture was discontinued. She was mobilized and was able to walk with assistance. The ulcer healed. For 2 months (weeks 40 to 48) she was given a codeine and propoxyphene compound. At weeks 49 to 50 increasingly severe back pain related to progression of her disease led to reinstitution of therapy with the Brompton mixture, the dose of morphine temporarily being high. Radiation therapy again relieved the pain and the dose of morphine was tapered. At 60 weeks the narcotic mixture was once again discontinued. No symptoms related to narcotic withdrawal were noted.

Case 2: A 52-year-old woman with lumbar back pain, weakness, lower limb edema and anemia related to disseminated carcinoma of the cervix had been managed with parenteral morphine for 6 weeks when she was transferred for further care to the Royal Victoria Hospital's palliative care unit. Therapy with the Brompton mixture was instituted and gave excellent results (Fig. 3). She is presently able to be up in a chair and is pain-free; the doses of morphine in the mixture are being decreased.

Case 3: A 78-year-old man with prostatic carcinoma was admitted to hospital with incapacitating back pain. Therapy with the Brompton mixture was instituted (Fig. 4). The prompt ensuing relief enabled his return home for 14 weeks. During this time he was up and about and was able to enjoy his garden. He was then readmitted to hospital with increased pain and increasing spinal cord compression, resulting in paraplegia. Increasing the dosage again controlled his pain and he was able to be cared for at home for the final 10 weeks of his life.

These cases illustrate the use of the Brompton mixture for periods ranging from 9 weeks to more than 1 year. In all three there was complete pain control, increased mobility, and an absence of drug-induced somnolence, personality change or dose escalation.

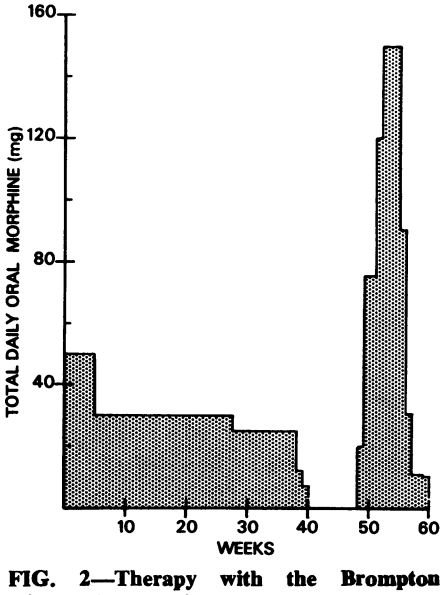

FIG. 2—Therapy with the Brompton mixture in case 1.

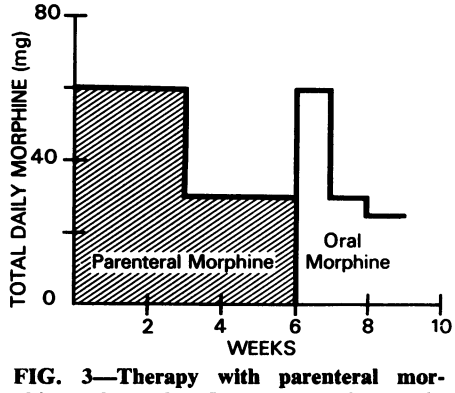

FIG. 3—Therapy with parenteral morphine, then the Brompton mixture in case 2.

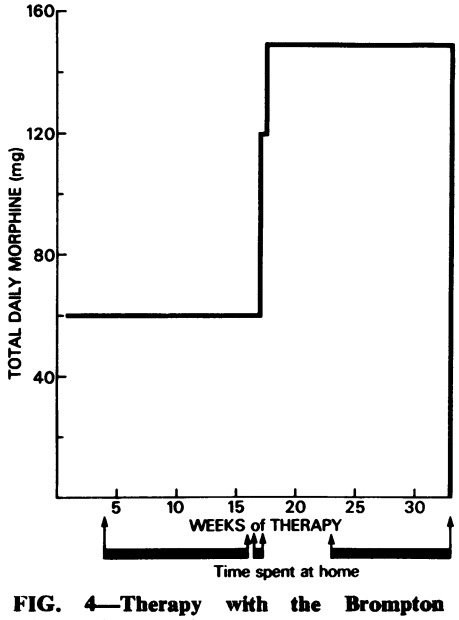

FIG. 4—Therapy with the Brompton mixture in case 3.

Additional measures

The Brompton mixture, to be effective against the "total pain" of advanced malignant disease, must be used in combination with other therapies. Symptom control may require additional measures such as radiotherapy, peripheral nerve or intrathecal block, neurosurgery, or physical measures such as splinting and passive exercises. Tricyclic antidepressants, benzodiazepines, anti-inflammatory agents (e.g., phenylbutazone), corticosteroids and hypnotics can all be useful in attacking the vicious circle of chronic pain. Environmental manipulation can also decrease pain. Melzack, Ofiesh and Mount, in their evaluation of the Brompton mixture (page 125 of this issue of the Journal), have suggested the importance of creating a pleasant, supportive environment in which a patient is able to communicate his concerns and where the resources of an interdisciplinary team are available to help in areas of interpersonal, psychosocial and philosophical need. Their study confirms our clinical experience that morphine, given in the form of the Brompton mixture with a phenothiazine, is a highly effective, flexible, safe and convenient means of controlling the chronic pain of malignant disease.

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