ANOTHER LOOK AT ANALGESICS IN PALLIATIVE CARE
Margaret Ellam, Consultant in Palliative Care
St John’s Hospice, Lancaster

INTRODUCTION
To the general public the figures are stark.
• One third of the population of the UK develops cancer.
• One quarter of the population of the UK dies of cancer.
• To the layman a cancer death is inevitably a painful one.

What is palliative care?
“Palliative” is derived from the Latin word “pallium” meaning a cloak or cover. In palliative care symptoms are “cloaked” with treatments which will promote patient comfort. There is no reason to wait until the patient has far-advanced disease before attempting to palliate symptoms, particularly pain. The Calman-Hine Report[1] recognised that palliative care should be available to all cancer patients from the time of diagnosis. Palliation of symptoms is equally appropriate in advanced non-malignant conditions.

Scale of the pain problem
Contrary to widely-held belief, pain and advanced cancer are not synonymous. Up to 75% of cancer patients will experience pain, ie 25% of cancer patients have no pain[2].

Reports of the WHO Method for Relief of Cancer Pain indicate that pain can be completely relieved in 80-90% of patients, and that “acceptable relief is possible in most of the remainder”[3]. The analgesic ladder (Figure 1) provides a scheme for introducing increasingly potent analgesics[4].

1 non-opioids: eg paracetamol, aspirin
2 weak opioids: eg codeine, dextropropoxyphene
3 strong opioids: eg morphine, fentanyl

Adjuvant drugs are those that control the unwanted side-effects of the analgesic (eg laxatives) or those that enhance the analgesic effect, eg cortico steroids

MORPHINE IS THE GOLD STANDARD AND USED CORRECTLY IT IS SAFE AND EFFECTIVE

Using these medications in a sequential manner does indeed control cancer pain for the great majority of patients. But what about the 10-20% of patients whose pain is not completely relieved, or whose relief is not “acceptable”? To understand current ideas about analgesics it is helpful to consider pain mechanisms[5] (Figure 2).

Physiological pain
In the figure a brief painful stimulus causes transmission of a nerve impulse along sensory fibres into the central nervous system and pain is experienced. Such pain provides warning and protection for the individual’s survival. The mechanisms involved in transmitting and processing the information are straightforward.

Pathological pain
Persisting stimuli, as for example fractures, abscesses or liver capsule stretch, cause peripheral nerve endings to become hypersensitive. Nociceptors in the surrounding area show increased excitability and can be activated by innocuous stimuli. Similar changes happen in the dorsal horn of the spinal cord and the CNS moves to a more excitable state. Pain is felt as more severe and continuous. Both physiological and pathological pains are easily understood by patients and professionals. Pathological pain is usually easy to control with analgesics.

Neuropathic pain
Neuropathic pain results from dysfunction or injury in the peripheral or central nervous system. It has also been called ‘non-nociceptive pain’, reflecting the observation that harmless stimuli at the periphery (such as touch) are felt as pain by the patient. After transmission of the impulse through abnormal nervous tissue, distortion of the information produces a painful sensation. In addition, there is amplification of the impulse (see below – “windup”) and the pain is particularly severe and distressing. Typically the patient apologises for complaining of ‘a severe pain in a numb area’. Patients understand numbness but are confused by the accompanying pain. Examples include post-herpetic
neuralgia, brachial plexopathy or thalamic syndrome. Light touch, such as the pressure of bed clothes or a doctor’s gentle examination, can produce excruciating pain.

Whereas most pathological pains respond to morphine, many neuropathic pains may be partially or completely morphine-insensitive. Most cancer pains that are difficult to treat will fall into this category. But ‘old-fashioned’ medications are proving helpful – paracetamol, ketamine and methadone.

PARACETAMOL

Because paracetamol is so readily available in “over the counter” preparations its role in complex pain management is often overlooked. Paracetamol (like NSAIDs) is a cyclooxygenase inhibitor which reduces prostaglandin production. Prostaglandins are thought to sensitise nociceptors to other mediators. However, unlike aspirin, diclofenac etc which reduce prostaglandin production at peripheral nerve endings, paracetamol inhibits brain cyclo-oxygenase. It is therefore quite logical to combine paracetamol with an NSAID for better analgesia, getting benefit from peripheral and central anti-prostaglandin action. It is common for a patient with neuropathic pain to observe “Your morphine doesn’t work but two Co-Codamol tablets give me a bit of relief’. The paracetamol is the active agent in that situation.

KETAMINE

Ketamine is an intravenous general anaesthetic agent which enjoyed popularity a few decades ago. Problems with side-effects, especially emergence phenomena, caused it to be relegated to use in battlefield or major accident situations. However, in subanaesthetic doses it is a useful analgesic for neuropathic pain, achieving its effect through NMDA (N-methyl D-aspartate) receptor antagonism.

NMDA receptors and ‘windup’ Repeated stimuli passing along damaged C nerve fibre (see neuropathic pain in Figure 2) cause escalating responses in receptor cells in the dorsal horn of the spinal cord. Chemical transmitters affecting the NMDA receptor are thought to produce this ‘windup’ effect. NMDA receptor block will produce analgesia.

Practical points in ketamine use

1. Only a parenteral formulation is available. It can be used in a syringe driver – dose range 150-600mg/24hours. The parenteral form can be taken orally, but taste is unpleasant. Doses start at 20mg six hourly.

2. Major disadvantage is unpleasant psychomimetic side-effects eg nightmares, hallucinations. These can be prevented by concurrent use of benzodiazepines or haloperidol.

3. Cardiovascular stimulation can occur leading to tachycardia and hypertension.

4. Should be avoided in raised intracranial pressure or seizures.

5. Ketamine is available in hospitals and hospices. In the community it is necessary to order Ketamine on a named-patient basis from the manufacturers, Parke-Davis.

6. At present, patients are usually stabilised on oral Ketamine as in-patients in the hospice and then discharged into the community. Local GPs have needed help and advice on ordering supplies of ketamine.

Case Study

Mrs P. Aged 65 years. Had disseminated bone metastases from carcinoma of the kidney. She had exhausted chemotherapy. She presented with severe pain affecting L5/S1 dermatomes unresponsive to all medication. CT scanning showed destruction of the left side of the sacrum. Whilst waiting for radiotherapy she became pain-free on ketamine 30mg qds.

Opioid rotation and Methadone

Some patients who have poor pain control on morphine may benefit from trying an alternative strong opioid eg methadone. Such ‘opiod rotation’ is currently popular, especially in the USA. These patients have pain that experience suggests should be morphine-sensitive (‘pathological’ in previous diagram) or they may have typical neuropathic pain.

Other patients may get pain relief from morphine, but develop intolerable side effects. This is particularly true of patients in renal failure. They are difficult to manage on morphine because of accumulation of active morphine metabolites.

Diacetyl morphine (diamorphine)
Clinical Focus: Pain Management

One hundred years ago the *Lancet* reported “of all the lessons which were hammered into me during my hospital career none was more persistently driven home than the fact that it is extremely dangerous to administer morphine in kidney disease”\(^7\). This still holds true. Patients who were previously stable on a dose of morphine must be suspected of having developed renal failure if they become morphine toxic.

So for two groups of patients (those apparently resistant to morphine, and those unable to tolerate its side effects) an alternative strong opioid may be tried. Methadone is the current favourite.

**METHADONE**

Methadone is a synthetic strong opioid which has been available for over fifty years. It has a broader range of opioid receptor action (mu and delta) than does morphine (mu only) and also has some NMDA receptor activity. It should then, like ketamine, be helpful in neuropathic pain.

It is a difficult drug to use, as it may take between four and seven days to reach a stable state. During that period the patient needs to take methadone 3-hourly pm. When pain is controlled a bd or tds regimen can be started.

**Conversion from morphine to methadone**

- Total daily dose of morphine is calculated (EDDM)
- When patient’s pain is controlled (3-7 days) calculate total daily dose of methadone
- Divide by two or three for bd or tds regimen
- Again, we would want to admit patients to the hospice to titrate up the dose

**Topical diamorphine**

Research suggests opioid receptors exist at peripheral nerve endings. They are synthesised in the dorsal root ganglion of C fibres and are relayed out to the periphery. Why give large doses of opioid to a patient if a much smaller dose can be applied directly to a painful lesion? Small doses of diamorphine (5-10 mgm) mixed with a hydrocolloid (eg Intrasite) can be applied to painful lesions such as pressure sores, which are then covered with an occlusive dressing. Analgesia is long-lasting (up to 25 hours) and free from systemic side-effects.

**CONCLUSION**

Pain is a psychosomatic experience. Aristotle, who described the five basic senses, called pain a “passion of the soul”. He indicated that it is not only a sensory experience but also has an emotional component.

Neurophysiologists continue to reveal the complex nature of pain sensation and to provide mechanisms for blocking main pathways.

For our part, we must remember to see the pain in the context of the whole patient.

**REFERENCES**

4. World Health Organisation *Cancer Pain Relief* 1986