

*ABC of palliative care***The last 48 hours**

Jim Adam

During the final 48 hours of life, patients experience increasing weakness and immobility, loss of interest in food and drink, difficulty swallowing, and drowsiness. With an incurable and progressive illness, this phase can usually be anticipated, but sometimes a deterioration can be sudden and distressing. Control of symptoms and family support take priority, and the nature of the primary illness becomes less important. This is a time when levels of anxiety, stress, and emotion can be high for patients, families, and other carers. It is important that the healthcare team adopts a sensitive yet structured approach.

Principles

An analytical approach to symptom control continues but usually relies on clinical findings rather than investigation. This approach spans all causes of terminal illness and applies to care at home, hospital, or hospice.

Drugs are reviewed with regard to need and route of administration. Previously "essential" drugs such as antihypertensives, corticosteroids, antidepressants, and hypoglycaemics are often no longer needed and analgesic, antiemetic, sedative, and anticonvulsant drugs form the new "essential" list to work from. The route of administration depends on the clinical situation and characteristics of the drugs used. Some patients manage to take oral drugs until near to death, but many require an alternative route. Any change in medication relies on information from patient, family, and carers (both lay and professional) and regular medical review to monitor the level of symptom control and side effects.

This review should include an assessment of how the family and carers are coping; effective communication with all involved should be maintained and lines of communication made clear and open. The knowledge that help is available is often a reassurance and can influence the place of death.

Symptom control**Pain**

Pain control is achievable in 80% of patients by following the World Health Organisation's guidelines for use of analgesic drugs, as outlined in the first chapter of this series. A patient's history and examination are used to assess all likely causes of pain, both benign and malignant. Treatment (usually with an opioid) is individually tailored, the effect reviewed, and dose titrated accordingly. Acute episodes of pain are dealt with urgently in the same analytical fashion but require more frequent review and provision of appropriate "breakthrough" analgesia. If a patient is already receiving analgesia then this is continued through the final stages; pain may disturb an unconscious patient since the original cause of the pain still exists.

If oral administration is no longer possible the subcutaneous route provides a simple and effective alternative. Diamorphine is the strong opioid of choice because of its solubility and is delivered through a syringe driver device to avoid repeated injections every four hours. It can be mixed with other "essential" drugs in the syringe driver. Rectal administration is another alternative, but the need for suppositories every four hours in

Principles of managing the last 48 hours

- Problem solving approach to symptom control
- Avoid unnecessary interventions
- Review all drugs and symptoms regularly
- Maintain effective communication
- Ensure support for family and carers

Routes of administration of drugs for last 48 hours**Oral***All drug types***Sublingual***Antiemetic*Hyoscine hydrobromide 0.3 mg/6 hours (Kwells)
Prochlorperazine 3-6 mg/12 hours*Sedative or anxiolytic*

Lorazepam 0.5-2 mg/6 hours (fast acting and short duration)

Transdermal*Opioid*

Fentanyl (only if patient already using patches)

Antiemetic

Hyoscine hydrobromide 0.5 mg/72 hours (Transcop)

Subcutaneous**Opioid*

Diamorphine (individual dose titration)

Non-steroidal anti-inflammatory drug

Diclofenac (infusion) 150 mg/24 hours

*Antiemetics*Cyclizine† 25-50 mg bolus every 8 hours, up to 150 mg/24 hours
Metoclopramide‡ 10 mg bolus every 6 hours, 40-80 mg/24 hours
Hyoscine hydrobromide‡ (also dries secretions) 0.4-0.6 mg bolus, up to 2.4 mg/24 hours
Methotrimeprazine‡ (also sedative at higher doses) 25 mg/ml ampoule, 6.25-25 mg bolus, 6.25 mg titrated up to 250 mg/24 hours via syringe driver*Sedative*Haloperidol‡ (also useful for confusion with altered sensorium) 2.5-5 mg bolus, 5-20 mg/24 hours
Midazolam‡ (anxiolytic at smaller doses, anticonvulsant) 2.5-10 mg bolus, 5-60 mg/24 hours*Somatostatin analogue*

Octreotide‡ (for large volume vomit associated with bowel obstruction) 150-600 µg/24 hours

Rectal*Opioid*Morphine (individual dose made by pharmacist taken every 4 hours)
Oxycodone 30-60 mg/8 hours*Non-steroidal anti-inflammatory drug*

Diclofenac 100 mg once daily

*Antiemetic*Prochlorperazine 25 mg twice daily
Domperidone 30-60 mg/6 hours
Cyclizine 50 mg/8 hours
Chlorpromazine (also sedative) 100 mg/8 hours (equivalent to 50 mg/8 hours orally)*Sedative*

Diazepam (also anxiolytic and anticonvulsant) rectal tubes 5-10 mg

*All subcutaneous preparations diluted in sterile water except diclofenac (0.9% saline)

†Compatible with diamorphine but liable to precipitate as concentrations increase

‡Compatible with diamorphine

the case of morphine limits its usefulness. Oxycodone suppositories (repeated 8 hourly) may be more practicable.

Longer acting opioid preparations (transdermal fentanyl and sustained release morphine) should not be started in a patient close to death; there is a variable delay in reaching effective levels, and, since speedy dose titration is difficult, they are unsuitable for situations where a rapid effect is required, such as uncontrolled pain. If a patient is already prescribed fentanyl patches these should be continued as baseline analgesia; if pain escalates additional quick acting analgesia (immediate release morphine or diamorphine) should be titrated against the pain.

Not all pains are best dealt with by opioids. For example, bone pain may be helped by a non-steroidal anti-inflammatory drug, while muscle spasm may be eased by diazepam. Non-drug measures still apply: for example, pain from a dry mouth requires mouth care; a pressure sore requires a change of position, a comfort dressing, local anaesthetic gel, and an appropriate mattress; and a distended bladder and loaded rectum require catheterisation and rectal evacuation respectively. It is also important to remember all the non-cancer pains, new and old, that may be present.

Breathlessness

The scope for correcting "reversible" causes of breathlessness becomes limited. A notable exception is cardiac failure, for which diuresis may be effective. In most cases the priority is to address the symptom of breathlessness and the fear and anxiety that may accompany it.

General supportive measures should be considered in all cases. Face masks may be uncomfortable or intrusive at this time, but oxygen therapy may help some patients (even in the absence of hypoxia). Nebulised 0.9% saline is useful if a patient has a dry cough or sticky secretions but should be avoided if bronchospasm is present.

Opioids and benzodiazepines can be helpful and should be initiated at low doses. Immediate release morphine can be titrated to effect in the same way as for pain. If a patient is using morphine for pain control then a dose slightly higher than the appropriate breakthrough dose (oral or parenteral) is usually required for treating acute breathlessness. The choice of anxiolytic is often determined by what is the most suitable route of administration, but the speed and duration of action are important.

Noisy respiration may be helped by repositioning the patient and, if substantial secretions are present, hyoscine hydrobromide (0.4-0.6 mg subcutaneous bolus or up to 2.4 mg/24 hours via syringe driver). Occasionally, gentle suction may be required. End stage stridor is managed with opioids and anxiolytics, when it is usually too late for corticosteroids.

Restlessness and confusion

These may be distinct entities or they may overlap. A problem solving approach is essential. The threshold for discomfort and disorientation is often lowered in cachectic or anxious patients. Attention to a patient's surroundings is therefore important—a stable, comfortable, and safe environment should be fostered; soft light, quiet, and familiar faces are reassuring.

The key to treatment lies in calming the acute state while addressing the cause, if apparent and appropriate. A notable example is the mental clouding, hallucinations, confusion, and restlessness associated with opioid toxicity, which can be eased with haloperidol while the opioid dose is reviewed. In general, choice of drug treatment depends on the likely cause. Doses are titrated up or down to achieve the desired effect, and the situation should be reviewed regularly and often until the acute

Opioid treatment for pain control

Starting dose—Immediate release morphine 5 mg every 4 hours by mouth

Increments—A third of current dose (but varies according to "breakthrough analgesia" required in previous 24 hours). For example, immediate release morphine 15 mg every 4 hours by mouth is increased to 20 mg/4 hours

Breakthrough analgesia—A sixth of 24 hour dose. For example, with diamorphine 60 mg delivered subcutaneously by syringe driver over 24 hours, give diamorphine 10 mg subcutaneously as needed for breakthrough pain

Conversion ratio—Morphine by mouth (or rectum) to subcutaneous diamorphine is 3:1. For example, sustained release morphine 30 mg every 12 hours by mouth plus three doses of immediate release morphine 10 mg by mouth gives total dose of oral morphine 90 mg every 24 hours; convert to diamorphine 30 mg/24 hours delivered subcutaneously

Management of breathlessness

- Reverse what is reversible
- General supportive measures—Explanation, position, breathing exercises, fan or cool airflow, relaxation techniques
- Oxygen therapy
- Opioid
- Benzodiazepine
- Hyoscine
- Nebulised saline (if no bronchospasm and patient able to expectorate)



Non-drug measures which can help a breathless patient

Causes of restlessness and confusion

- Drugs—Such as opioids, corticosteroids, neuroleptics, alcohol (intoxication and withdrawal)
- Physical—Unrelieved pain, distended bladder or bowel, immobility or exhaustion, cerebral lesions, infection, haematological, major organ failure
- Metabolic upset—Urea, calcium, sodium, glucose, hypoxia
- Anxiety and distress

episode settles. Highly agitated patients may need a large dose, and continuous infusion may be needed. Rectally administered drugs are possible alternatives. Explanation and support for the relatives and carers are paramount at this time.

If a patient is experiencing distressing twitching or jerks then metabolic disorders, opioid toxicity, or drugs that lower seizure threshold should be considered. A review of medication and treatment with a benzodiazepine or anticonvulsant (such as clonazepam orally, diazepam rectally, or midazolam subcutaneously) is indicated. Anxiety or distress not responding to general supportive measures may be helped by diazepam or midazolam, but it should always be remembered that a patient may be suffering from an emotional or spiritual anguish that cannot be relieved by drugs.

Nausea and vomiting

If antiemetics have been needed within the previous 24 hours then continuation is advisable. Nausea and vomiting may rarely occur as a new symptom at this time (< 10% of cases), and treatment of the likely cause is preferred if this is practical in the clinical situation, otherwise an appropriate antiemetic should be selected. If the aetiology is unclear then choose a centrally acting or broad spectrum antiemetic in the first instance.

Occasionally, more than one antiemetic is required if resistant vomiting of a multifactorial cause exists. Subcutaneous administration of antiemetics is preferable, but suppositories (such as prochlorperazine, cyclizine, or domperidone) may be useful if no syringe driver is available. Antiemetic treatment that has been initiated for bowel obstruction should be continued.

Emergency situations

Appropriate and timely action has an important immediate effect on patients and families. It can also influence bereavement and future coping mechanisms of both lay and professional carers. Emergencies can sometimes be anticipated: thus, previous haemoptysis may predict haemorrhage, bone metastases predict pathological fracture, enlarging upper airway tumour predict stridor, and previous hypercalcaemia predict confusion.

Some emergencies may be preventable. For example, a patient with a brain tumour who can no longer take corticosteroids may have a seizure unless anticonvulsant treatment is maintained: subcutaneous infusion of midazolam (starting at 30 mg/24 hours) and rectally administered diazepam (10 mg) may be the strategy required.

However, most emergencies in the last 48 hours are irreversible, and treatment should be aimed at the urgent relief of distress and concomitant symptoms. Drugs should be made available for immediate administration by nursing staff without further consultation with a doctor. Directions regarding use should be written clearly in unambiguous language. Useful drugs are injections of midazolam (5-10 mg if patient not previously exposed to benzodiazepine, otherwise titrate as appropriate) and diamorphine (5-10 mg if no prior exposure to opioid, otherwise a sixth to a third of the 24 hour dose).

Haemorrhage is distressing and memorable for both patients and carers. Haemoptysis, haematemesis, and erosion of a major artery such as the carotid are visually traumatic. The prompt use of drugs, dark coloured towels to make the view less distressing (green surgical towels in hospital), and warmth will aid comfort. In these situations death may occur quickly. A supportive presence is helpful, and explanations to patients and their carers of what is being done will help minimise distress in a crisis.

Management of restlessness and confusion

- Treat the acute state and address cause
- General supportive measures—Light, reassurance, company
- Choice of drug treatment relates to likely cause

Drugs

- Haloperidol
Indications—Drug toxicity, altered sensorium, metabolic upset
Dose—Oral drug 1.5-3 mg, repeat after 1 hour and review; subcutaneous bolus 2.5-10 mg; subcutaneous infusion 5-30 mg over 24 hours
- Midazolam
Indications—Anxiety and distress, risk of seizure
Dose—Subcutaneous bolus 2.5-10 mg; subcutaneous infusion 5-100 mg over 24 hours
- Methotrimeprazine
Indications—Need for alternative or additional sedation
Dose—Subcutaneous bolus 25 mg; subcutaneous infusion up to 250 mg over 24 hours (lowers seizure threshold, use with care)
- For altered sensorium plus anxiety, combine haloperidol and midazolam
- Avoid “slippery slope” of inappropriate sedation in patient who needs to talk—So called terminal agitation can result from the inappropriate use of drugs

Causes and treatment of nausea and vomiting

Site of effect	Treatment
<i>Drugs or biochemical upset</i>	
Chemoreceptor trigger zone (area postrema) via dopamine receptors	Haloperidol
<i>Raised intracranial pressure</i>	
Vomiting centre(s) via histamine receptors	Cyclizine
<i>Multifactorial or uncertain</i>	
Various	Methotrimeprazine
<i>Gastrointestinal stasis</i>	
Gastrokinetic	Metoclopramide Cisapride
<i>Bowel obstruction</i>	
Vomiting centre(s) via vagus nerve	Cyclizine
Gastrointestinal secretions	Octreotide Hyoscine butylbromide

Emergencies

- Stridor
- Seizure
- Haemorrhage
- Pain
- Confusion



Patient with ulcerated neck tumour is at risk of erosion of the carotid artery and massive bleed

Support

Support means recognising and addressing the physical and emotional issues that may face patients, families, and carers during this time. Honesty, listening, availability, and assurance that symptom control will continue are valued by patients and carers. Fears or religious concerns should be acknowledged and addressed appropriately, and respect for cultural differences should be assured. Explain what is happening, what is likely to happen, the drugs being used, the support available, and how the family can help with care.

Lack of practical support is one of the commonest reasons for admission to hospital or hospice at this time, and, therefore, consideration should be given to extra help—such as Marie Curie nurses (organised through the district nursing service) to give carers rest and support. An assessment of the risk of bereavement allows care to be planned for the family after the patient's death. Professional carers may also need support, particularly if the last 48 hours have been difficult, and this requires an open line of communication.

Risk factors for bereavement

Patient—young
Illness—Short, protracted, disfiguring, distressing
Death—Sudden, traumatic (such as haemorrhage)
Relationship—Ambivalent, hostile, dependent
Main carer—Young, other dependants, physical or mental illness, concurrent crises, little or no support

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The ABC of palliative care is edited by Marie Fallon, Marie Curie senior lecturer in palliative medicine, Beatson Oncology Centre, Western Infirmary, Glasgow, and Bill O'Neill, science and research adviser, British Medical Association, BMA House, London. It will be published as a book in June 1998.

Any questions

Combination approach to pain relief

What analgesia could be used for a patient who is hypersensitive to opiates, which include morphine, pethidine, and oral codeine? The patient feels very unwell and develops low blood pressure. What analgesia should be used in the event of an accident or postoperatively? Is there a case for a challenge test when the patient is well?

I will limit my response to the management of acute pain. As a consequence of an intercollegiate report (and other guidelines) most acute surgical hospitals now offer an acute pain service led by a consultant anaesthetist.^{1 2} The first action might be to contact the local pain service, which should be able to advise on the special needs of the patient.

The symptoms described are common and multifactorial, so the next step should be to establish that they are related to opioid treatment. One approach might be to institute a placebo controlled opioid challenge in hospital. But a patient's response to opioids is very different in the pain free setting and a challenge is not necessarily a reliable predictor. If the patient is sensitive to opioids the solution may simply be to find the opioid which best suits him or her, although the evidence that equianalgesic doses of different opioids vary in their side effect profile is not great.³ Pethidine, by virtue of its metabolite norpethidine, is particularly prone to inducing serious toxicity to the central nervous system, especially in patients with renal failure, and thus has no role in pain management.^{2 3} Some high potency opioids—for example, fentanyl—do have a reputation for producing less cardiovascular side effects than “older” opioids. Their use has hitherto been restricted to surgical anaesthesia, but they are now finding a place outside the operating theatre.

Sophisticated techniques of opioid administration, while not appropriate in all patients, may help the patient. A particular advance has been patient controlled analgesia.^{1 2} This involves parenteral drug

delivery via a device, which allows the patient to self administer small preset boluses from a reservoir. One advantage of this biological feedback system is that the delivered dose is titrated to the individual requirement of the patient. Consequently, the plasma concentration of opioid is more likely to remain within the therapeutic range, when compared with intermittent nurse administered injections.

The recent advent of parenteral preparations of potent non-steroidal anti-inflammatory drugs means that these drugs are now finding a place in acute pain management. While their relatively low analgesic efficacy limits their use as a sole analgesic after major surgery, they may usefully be combined with patient controlled analgesia. The safety of perioperatively administered non-steroidal anti-inflammatory drugs has yet to be fully established.

Finally, regional anaesthesia offers an underused alternative to systemic opioid analgesia, particularly for wounds of the trunk or limbs.^{1 2} Catheters may be placed in the epidural space or brachial plexus sheath to allow continuous infusion of local anaesthetic over several days. A useful approach is epidural delivery of a combination of local anaesthetic and opioid, the advantage being that the opioid can be delivered at a high concentration directly to its spinal site of analgesia. This combination approach limits not only the systemic side effects of opioids, but also the motor block associated with local anaesthetics.

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- 2 United States Department of Health and Human Services. *Acute pain management: operative or medical procedures and trauma*. Rockville, Maryland: United States Department of Health and Human Services, 1992.
- 3 McQuay HJ, Moore RA, Justins DM. Treating acute pain in hospital. *BMJ* 1997;314:1531-5.