Palliative sedation therapy

It is sometimes not possible to relieve symptoms adequately in dying patients. When all other remedies have failed, sedation can be a useful means to relieve terminal suffering. When used appropriately, palliative sedation does not, and should not, shorten life.

Palliative sedation is the use of drug therapy to allow the dying patient to be less aware of distressing symptoms. The need to address intolerable symptoms in terminally ill patients is imperative, and fortunately most symptoms in dying patients can be successfully controlled by good medical and nursing care. Occasionally, however, there are symptoms which ultimately prove resistant to any further palliation. A thorough assessment of the patient should be made to identify reversible causes of distress, but it is not possible in all cases to adequately relieve pain, breathlessness, and psychological or spiritual angst. As a means of last resort, sedation can then be used in order to render the patient less aware of his/her symptoms and thereby reduce suffering.

Until recently the terminology describing palliative sedation has been confusing. This has led to conflicting evidence about its frequency and indications for use, and may have contributed to the moral controversy among some physicians and ethicists (Craig, 1994, 1996; Billings and Block, 1996). An international panel concluded that an accepted definition for the term palliative sedation therapy should be:

> **'The use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction of patient consciousness.' (De Graeff and Dean, 2007)**

Table 1. Potentially treatable causes of terminal agitation and initial management

Cause	Examples	Investigations/management
Drug toxicity or withdrawal	Antidepressants, opioids, steroids, benzodiazepines, alcohol and nicotine withdrawal	Drug history, stop or replace causative drug if possible, replacement therapy where appropriate. Antipsychotic/ sedative drugs if needed
Metabolic upset	Infection, hypoxia, renal failure, hepatic failure, electrolyte imbalance (e.g. hypercalcaemia)	Blood test screening and reversal of cause if possible and appropriate
Other physical causes	Pain, colic, urinary retention, faecal impaction, breathlessness, raised intracranial pressure	Physical examination and management of underlying cause
Psychological or emotional	Fear of death and dying, unresolved social/psychological/ spiritual issues. Dementia	Safe and supportive environment. Ongoing assessment and therapy where possible

Dr Bill Hulme *is Specialist Registrar in Palliative Medicine, Leeds General Infirmary, Leeds LS1 3EX and* **Dr Colin Campbell** *is Consultant in Palliative Medicine, St Catherine's Hospice, Scarborough*

Correspondence to: Dr B Hulme

How do you decide if symptoms are refractory?

Symptoms are refractory if they persist despite all possible treatments being given. A particular challenge when time is limited is that patients may be too frail to be subjected to extensive investigations and therapies, or not live long enough to benefit from them. In addition patients may decide to refuse such interventions. This may include treatments such as surgery, chemotherapy or radiotherapy.

Deciding whether a symptom is refractory can be difficult. As the use of sedation is a treatment of last resort, all other means of alleviating distress must have been tried or excluded (*Table 1*). A refractory symptom is not simply one that is difficult to treat.

The most common symptom in the last days of life that necessitates palliative sedation therapy is delirium, often with restlessness (so-called 'terminal restlessness'). This can be undignified for the patient and distressing for relatives and carers. Other symptoms where palliative sedation therapy is indicated are pain, nausea and vomiting, breathlessness and uncontrollable seizures (De Graeff and Dean, 2007). Occasionally sedation has to be given as an emergency, such as for massive haemorrhage, where a rapid reduction in consciousness is required to reduce patient distress.

The role of sedation to relieve non-physical symptoms is more controversial. Psychological and so-called 'existential' suffering (including symptoms of hopelessness, remorse and meaninglessness) can contribute to the total suffering of a patient. However, treatment for this is often more complex and multidisciplinary, and therefore difficult to label as refractory. As a result sedation for these symptoms is rarely used, and should only be initiated after careful consultation including expert opinion (Morita et al, 2000; Rousseau, 2001).

Commencing palliative sedation therapy

Nearly all palliative sedation therapy is given in the last few days of life, but recognizing that the patient is actually dying can be difficult (Ellershaw and Ward, 2003). Many units now use the Liverpool Care of the Dying pathway, which uses criteria to help with the diagnosis of dying in a variety of conditions (Ellershaw and Wilkinson, 2003).

It is common for patients in the last few days of life to lack the mental capacity to understand and make complex medical decisions about their care. The Mental Capacity Act 2005 states that health-care providers must presume the patient has the mental capacity to make a decision unless it is proven otherwise. It is also up to the treating team to ensure all appropriate measures have been taken to optimize the likelihood of the patient achieving the required mental capacity to make treatment decisions (National Council for Palliative Care, 2008). If the patient is felt unable to make an informed decision about receiving palliative sedation therapy, a 'best interests' decision needs to be made by the treating team. This should take into account views of 'those close to the patient', who may include family but also professional carers, as to what they think the patient's wishes and preferences might have been in these circumstances. The patient may have previously appointed a lasting power of attorney for this decision-making role.

How do you give sedation?

Having decided that palliative sedation therapy is the most appropriate course of action, there are a number of drugs and routes of administration that can be used. The most commonly used drug for palliative sedation therapy is the benzodiazepine midazolam which has the following characteristics:

- Short half life
- Dose-dependent effects
- Parenteral administration (subcutaneously as this is safer than intravenous)
- Anxiolytic, anticonvulsant and muscle relaxant properties
- High therapeutic safety margin subcutaneously, but potentially additive respiratory depressant effect with strong opioids
- Can be reversed in an emergency with the specific antidote, flumazenil (Blanchet, 2006; De Graeff and Dean, 2007; Twycross and Wilcock, 2007).

Sedation can be given intermittently on an as-required basis, or by continuous subcutaneous infusion using a syringe driver. Initial doses should be small enough so that the patient can indicate how much benefit he/she is receiving, and the level of sedation can be titrated accordingly.

A means of monitoring the response to treatment should also be discussed, and how to titrate doses accordingly. For patients who are unable to communicate as a result of illness or sedation, this response is usually a bedside assessment looking for signs of grimacing, moaning or restlessness, which would indicate an insufficient level of sedation.

Three levels of sedation are recognized, with deeper sedation only being used if lighter levels are ineffective in relieving suffering (De Graeff and Dean, 2007):

1. Mild (somnolence) – where the patient is awake but with a lowered level of consciousness
2. Intermediate (stupor) – the patient is asleep but can be woken briefly
3. Deep (coma) – the patient is unconscious and unresponsive.

Drugs other than midazolam can be used in palliative sedation therapy, but are usually reserved for patients with particular problems. For patients with distress resulting from delirium, adequate doses of haloperidol can be used. Only after this treatment approach has failed, should the more sedating antipsychotic, levomepromazine, be tried, with or without midazolam.

For intractable seizures, or failure of conventional sedatives to control distress, phenobarbital is sometimes used. There is the potential for respiratory depression with this drug, and it should only be used with specialist guidance. *Table 2* outlines drugs, routes of delivery, appropriate doses and half lives.

Opioids such as morphine and diamorphine should not be used with the primary intent of causing sedation. Opioids are commonly used in the last days of life to manage pain and breathlessness, and often need to be given for these indications concurrently with sedatives such as midazolam. However, any sedating effect from opioids tends to be complicated by increasing delirium and myoclonic jerks, rendering them ineffective as sedatives (see *Case study*).

Ethical considerations in palliative sedation therapy

There have been a number of concerns in the past about the use of sedatives in patients at the end of life (Craig, 1994, 1996; Billings and Block, 1996; Baumrucker, 2002). Much of this has centred on a perceived lack of difference between using sedation until the point of death, and euthanasia. Palliative sedation therapy is quite distinct

Table 2. Sedative drugs used in palliative sedation therapy, with usual initial dose ranges

Drug	Half life	Usual initial dose range	Notes
Midazolam	2–5 hours	2.5–5 mg subcutaneously as required or 10–40 mg/24 h in a continuous subcutaneous infusion via a syringe driver	Also anticonvulsant properties
Levomepromazine	16–30 hours	6.25–12 mg subcutaneously as required or 25–50 mg/24 h in a continuous subcutaneous infusion via a syringe driver	Antipsychotic drug
Phenobarbital	48–144 hours	100–200 mg intramuscular bolus and 200–600 mg/24 h in a continuous subcutaneous infusion via a syringe driver	Also has anticonvulsant properties Potential to depress respiration Should only be given under specialist guidance

From Twycross and Wilcock (2007)

from euthanasia not least because of the intent that lies behind the act. In palliative sedation, the patient is sedated as he/she dies from his/her underlying disease, and this should not shorten life. However, in euthanasia, sedation is given with the express intent of significantly shortening life. The primary aim of palliative sedation therapy is to relieve distress, and with careful titration of sedatives this is achieved with no adverse effect on the patient's prognosis (Sykes and Thorns, 2003). As such, palliative sedation therapy is a proportionate intervention which does not require the significantly higher doses which would be needed to cause the patient's death. In those countries where there has been evidence of using disproportionate doses of sedation beyond what is needed to relieve suffering, this practice has been accurately described as 'slow euthanasia' (Billings, 1996; De Graeff and Dean, 2007).

Continuation or cessation of other treatments at the end of life

Throughout the course of a patient's illness, treatment plans should be regularly reviewed and a risk–benefit assessment made for each intervention. As the focus of care shifts from cure or stabilization of disease to palliation, it is common to stop treatments that are thought to be of little or no benefit. This may include drugs for secondary prevention of disease, such as statins or antihypertensives in patients thought to have a prognosis measured in weeks to months. Similarly the number of interventions required in the last few days of life is usually fewer than what is needed earlier in an illness.

Case Study

Mr A was a 77-year-old retired builder diagnosed with mesothelioma 1 year previously. Despite chemotherapy and radiotherapy the disease had encased the right lung and pleura, and had invaded through the chest wall. Tumour infiltration into intercostal nerves caused severe neuropathic pain around his chest which was poorly responsive to opioid and adjuvant analgesics. He also had marked breathlessness at rest, which pleural drainage and subsequent surgical pleurodesis failed to improve. He once confided that he had seen his father die 'in agony' from the same illness 20 years previously.

The hospital oncology team gradually titrated up his opioids for pain and breathlessness, but this failed to help and led to increasing confusion. A trial of antibiotics for a suspected chest infection did not improve his breathlessness and Mr A repeatedly pulled off oxygen masks saying he felt he was drowning.

After a consultation with the hospital palliative care team he agreed to trial the effect of midazolam (5 mg given subcutaneously), saying he just wanted to be 'free of this nightmare'. Thirty minutes later his overall levels of anxiety and distress were better, but he was still grimacing in pain.

Over the following 24 hours he had a total of 20 mg of midazolam given in as-required injections, which was converted to a 24 h subcutaneous infusion given via a syringe driver. The following day his condition had worsened and non-essential drugs were stopped. His requirements for midazolam to control his breathlessness and agitation increased, and he continued to show signs of distress until he was deeply sedated. He remained sedated until his death 4 days later, nursed on the Liverpool Care for the Dying pathway.

The decision to halt certain investigations and treatments often coincides with a decision to discuss, and possibly commence, palliative sedation therapy. They are, however, quite distinct decisions. For patients who commence palliative sedation therapy it may on occasions be in their best interests to continue other forms of treatment, most notably for symptom control. Life-prolonging treatments, including artificial hydration, may be appropriate to relieve thirst in individual cases. However, for most patients in the last days of life, parenteral fluids are unlikely to prolong life or relieve thirst, and may exacerbate peripheral oedema and respiratory secretions (Macfie, 2000; National Council for Palliative Care, 2007). Treatment decisions should therefore be made after an assessment of the risks and burdens to that individual, and monitored accordingly (General Medical Council, 2002).

For patients who are thought to be in the last days of life, the likelihood of successful resuscitation in the event of a cardiopulmonary arrest is very small. Such attempts at resuscitation are seen by many patients as undignified and inappropriate. Discussions about not attempting cardiopulmonary resuscitation and allowing a natural death should be held where appropriate and documented clearly in the patient's notes. However, when a clinical decision is made that cardiopulmonary resuscitation has no chance of success, it is not necessary or appropriate to initiate a discussion with the patient about it (British Medical Association, 2007).

Conclusions

Palliative sedation therapy has become an accepted and important aspect of end-of-life care where distressing symptoms cannot be managed by other means and the purpose of treatment is explicit to patient (if possible), carers and staff alike. It should only be initiated when all other options for treating symptoms have been exhausted. This should ideally be after consultation with the patient and may require input from specialist palliative care services.

Historically, opioids such as morphine and diamorphine were used to sedate but they can cause increased confusion, myoclonus and agitation. It is now common practice to use subcutaneous midazolam first line, with alternative sedatives in reserve for more refractory distress.

End-of-life care also involves consideration of withdrawing life-prolonging treatments that do not provide any symptom relief for the patient. The decision-making process to withdraw treatment is distinct from that of commencing palliative sedation therapy, and judgment should be made on a case-by-case basis. Where the relief of distressing symptoms comes at the cost of reduced consciousness from sedation, this should always be supported by good nursing care and close involvement with family and carers wherever possible. **BJHM**

Conflict of interest: Dr C Campbell is a member of the Association of Palliative Medicine's ethics committee; Dr B Hulme – none.

Baumrucker SJ (2002) Sedation, dehydration, and ethical uncertainty. *Am J Hosp Palliat Care* **19**(5): 299–300
Billings JA, Block S (1996) Slow Euthanasia. *J Palliat Care* **12**(4): 21–30
Blanchet V (2006) Sedation in the Management of Distress in End-Stage Diseases. www.sfap.org/pdf/III-O2b-pdf.pdf (accessed 4 November 2008)
British Medical Association (2007) *Decisions relating to cardiopulmonary resuscitation.* A joint statement from the British Medical Association, the Resuscitation Council (UK) and the Royal College of Nursing (www.bma.org.uk/images/DecisionsRelating ResusReport_tcm41-147300.pdf accessed 18 February 2009)
Craig GM (1994) On withholding nutrition and hydration in the terminally ill: has palliative medicine gone too far? *J Med Ethics* **20**(3): 139–43
Craig GM (1996) On withholding artificial hydration and nutrition from terminally ill patients. The debate continues. *J Med Ethics* **22**(3): 147–53
De Graeff A, Dean M (2007) Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. *J Palliat Med* **10**(1): 67–85
Ellershaw J, Ward C (2003) Care of the dying patient: the last hours or days of life. *BMJ* **326:** 30–4
Ellershaw J, Wilkinson S, eds (2003) *Care of the Dying - A Pathway to Excellence.* OUP, Oxford
General Medical Council (2002) *Withdrawing and withholding life-prolonging treatments: Good practice in decision-making*. General Medical Council, London
Macfie J (2000) Ethical and Legal considerations in the provision of nutritional support. *Curr Opin Clin Nutr Metab Care* **3:** 23–9
Morita T, Tsunoda J, Inoue S, Chihara S (2000) Terminal sedation for existential distress. *Am J Hosp Palliat Care* **17**(3): 189–95
National Council for Palliative Care (2007) *Artificial nutrition and hydration: Guidance in end of life care in adults.* National Council for Palliative Care, London
National Council for Palliative Care (2008) *The Mental Capacity Act in Practice: Guidance for end of life care.* National Council for Palliative Care, London
Rousseau P (2001) Existential suffering and palliative sedation: a brief commentary with a proposal for clinical guidelines. *Am J Hosp Palliat Care* **18**(3): 151–3
Sykes N, Thorns A (2003) Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med* **163**(3): 341–4
Twycross R, Wilcock A, eds (2007) *Palliative Care Formulary 3.* Palliativedrugs.com. Nottingham

KEY POINTS

- Palliative sedation reduces the dying patient's awareness of distressing symptoms.
- In each case, a thorough clinical assessment should first be made looking for treatable causes of distress.
- Sedation in dying patients should only be used where other treatment options have been exhausted or are not feasible.
- Midazolam is the first-line drug for palliative sedation.
- Opioids are often required for analgesia, but they may cause agitation, confusion and myoclonus if used for sedation alone.
- Comparisons between palliative sedation and euthanasia are unfounded because of their differing intentions and careful titration of sedation.