



Use of sedation to relieve refractory symptoms in dying patients

David Cameron, Douglas Bridge, Julia Blitz-Lindeque

Objectives. To document the use of sedation for refractory symptoms in patients admitted to an independent palliative care unit.

Method. A prospective descriptive study.

Setting. The 7-bed inpatient unit at Sungardens Hospice, Pretoria.

Subjects. Patients who required sedation for refractory symptoms in addition to normal palliative care treatment between January and June 2002.

Findings. Twenty of 100 consecutive patients admitted required sedation. All had advanced cancer. Their mean age was 68 years. Thirty-six per cent were men and 64% women.

Indications. Agitated delirium was the most common reason (45%) for using sedation, followed by intractable vomiting due to inoperable malignant intestinal obstruction in 25% of patients. Three patients with persistent convulsions or myoclonic jerking and 2 patients with severe refractory

dyspnoea required some sedation. Intractable pain was the main reason for sedation in only 1 patient.

Survival. Mean survival following the start of sedation was 92 hours/3.8 days (range 6 - 369 hours/0.25 - 19.4 days). The combined mean survival recorded in 9 other studies was 57 hours/2.4 days (range 36 - 93.6 hours/1.5 - 3.9 days).

Medication. The main drugs used for sedation were midazolam and haloperidol. The mean dosage for midazolam was 18.5 mg/24 hours (range 7.5 - 40 mg) and for haloperidol 8 mg/24 hours (range 5 - 10 mg).

For pain relief the mean daily dose of parenteral morphine was 76 mg (range 15 - 260 mg).

Conclusion. Use of sedation for the relief of refractory symptoms at Sungardens Hospice is in line with several studies reported in the international literature.

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Sedation in the context of terminal care has been a hotly debated topic for many years.^{1,4} In 1990 a report was published claiming that 52% of moribund patients required sleep-inducing sedation to control physical suffering.⁵ This stimulated a lot of discussion in palliative care circles, with many physicians being surprised at the apparent high percentage of patients needing sedation. Subsequent studies carried out in various centres throughout the world showed that the prevalence of sedation varied a great deal (1 - 72%).¹ It has been suggested that this wide variation can be attributed to differences in the terminology used, differences in the application of modern palliative care in different parts of the world and possibly varying standards and criteria for the use of sedation.^{1,6-8} Adding to the concern has been the accusation that in reality sedation of dying patients is the equivalent of

'slow euthanasia'.² There is therefore a need to clarify and carefully define the terms used with regard to sedation of dying patients, and to develop guidelines that are internationally recognised and accepted by both health professionals and the public.

Objectives

The aim of the study was to document the use of sedation for refractory symptoms in patients admitted to an independent palliative care unit.

Method

A prospective descriptive study was carried out of all patients admitted to Sungardens Hospice, Pretoria, between January and June 2002, whose symptoms were unresponsive to standard palliative care measures and who required sedation to relieve their distress.

Setting

Sungardens Hospice originated in 1987 as a nurse-led domiciliary service providing care for dying patients in the

Department of Family Medicine, University of Pretoria, and Honorary Medical Director, Sungardens Hospice, Pretoria

David Cameron, MB ChB, MPraxMed, MPhil (Palliative Medicine)

Royal Perth Hospital, Murdoch Community Hospice and University of Western Australia, Perth

Douglas Bridge, BMedSc (Hons), MB BS, FRACP, FRCP, FACHPM, DTM&H

Department of Family Medicine, University of Pretoria

Julia Blitz-Lindeque, BSc, MB ChB, MPraxMed



greater Pretoria area (population 1.48 million, 1996 census). It was based on the principles of the modern hospice movement developed in England during the 1960s under Dr Cicely Saunders at St Christopher's Hospice, London.

Sungardens Hospice gradually expanded and in 1990 a 7-bed inpatient unit (IPU) was opened to provide short-stay care for a wide range of terminal patients. In addition to terminal care, patients are also admitted for symptom control and occasionally to give the patient's family a period of respite. Three part-time doctors provide the medical care in the IPU.

Since 1998 an average of 218 patients have been admitted to the IPU each year. The majority (76%) of these patients have advanced cancer. Over the last few years the number of AIDS patients has increased steadily. By 2002, patients suffering from AIDS made up 12% of admissions and 33% of the patients in domiciliary care. The average length of stay in the IPU is 15 days and the Unit has a bed occupancy rate of 82%. One-third of the patients admitted are discharged to domiciliary care once their symptoms have been controlled.

Patient selection

All patients who received sedating drugs (apart from sleeping tablets) were included in the study. This selection can be criticised for being too broad.⁶ However, as the difference between sedation for mild anxiety or mild confusion and sedation for refractory symptoms is sometimes not clear-cut in dying patients, it was felt that the inclusion of all patients would minimise selection bias and underreporting.

The study began on 1 January 2002 and was completed on 15 June after 100 consecutive patients had been admitted. No patients or their families refused to participate in this research project.

Results

Patient profile

Twenty patients required sedation. All had advanced cancer. Their mean age was 68 years (range 49 - 88 years). The mean age of the whole group was 62.2 years (range 21 - 93 years). The slight difference was due to the younger ages (mean 32.2 years) of the 16 patients admitted with AIDS, none of whom required sedation. The gender ratio was 36% men and 64% women. This is very similar to the gender ratio (34:66) of the entire group of patients admitted during this period.

Reason for sedation

The main refractory symptoms requiring sedation were delirium (45%), nausea and vomiting (25%), convulsions (15%), dyspnoea (10%) and pain (5%) (Table I).

All patients had signs of very advanced cancer and had been

Table I. Refractory symptoms requiring the use of sedation in 20 patients admitted to Sungardens Hospice between January and June 2002

Refractory symptoms	Numbers	%
Agitated delirium	9	45
Intractable vomiting	5	25
Convulsions/myoclonic jerking	3	15
Severe dyspnoea	2	10
Pain	1	5

referred for palliative care. Malignant intestinal obstruction was present in 5 patients, 2 others had extensive bone metastases, 1 patient had severe jaundice, 1 had brain metastases, 2 patients had gastro-intestinal tract (GIT) bleeding and 1 had myoclonic jerking due to opioid-induced neurotoxicity.

Sedation — response and outcome

It took an average of 19 hours (range 1 - 96 hours, median 11.5 hours) for the sedation to be fully effective. Patients survived an average of 92 hours/3.8 days (range 6 - 369 hours/0.25 - 19.4 days) after sedation was started.

Medication used

Morphine sulphate and transdermal fentanyl were the only opioids used. For ease of comparison, the fentanyl dose was converted to its parenteral morphine equivalent (PME) according to the manufacturer's recommendation. The mean dosage of morphine used was 76.5 mg/24 hours (range 15 - 260 mg/24 h) (Table II).

For sedation, midazolam and haloperidol were the main drugs used. In all but 1 case these drugs were given by the subcutaneous (SC) route using a syringe driver. One patient was given midazolam intravenously because of sudden severe dyspnoea that was refractory to all other measures. In the 12 cases where midazolam was used, the mean dosage was 18.5 mg/24 hours (range 7.5 - 40 mg/24 h). Haloperidol was used in 13 cases, with a mean dosage of 8 mg/24 hours (range 5 - 10 mg/24 h).

Hydration

Four patients were receiving intravenous (IV) or SC fluids at the time sedation was started. These fluids were not discontinued. Four patients were able to continue some oral fluids, while the remainder received routine mouth care and had water sprayed frequently into their mouths. During this project, parenteral fluids were not commenced after sedation had begun. The possible use of IV or SC fluids was, however, discussed with all patients and their families before sedation. Their wishes were the main determining factor in deciding what should be done about maintaining hydration artificially.



Table II. Dosages of morphine, midazolam and haloperidol used at Sungardens Hospice compared with dosages used in four other studies

	Parenteral morphine equivalent (mg/24 h)	Midazolam (mg/24 h)	Haloperidol (mg/24 h)
Sungardens	Mean: 76.5 Range: 15 - 260 Number: 20 (100%)	Mean: 18.5 Range: 7.5 - 40 Number: 12 (60%)	Mean: 8 Range: 5 - 10 Number: 13 (65%)
Turner <i>et al.</i> ^{31*}	Mean: 66.5 Range: 0 - 360 Number: 43 (86%)	Mean: not stated Range: 2.5 - 47 Number: not stated	
Thorns and Sykes ^{32*}	Mean: 55.5 Range: not stated Number: 212 (89%)		
Morita <i>et al.</i> ^{33*}	Mean: 272/48 hrs (OME) [†] = 68/24 h (PME) Range: 1 - 6 240/48 h (OME) Number: 172 (82%)	Mean: 26 Range: 0.5 - 100 Number: 48 (23%)	Mean: 5 Range: 0.75 - 25 Number: 89 (43%)
Fainsinger [‡]		Mean: 33 Range: 5 - 180 Number: 69 (71%)	

*The studies by Turner *et al.*,³¹ Thorns and Sykes,³² and Morita *et al.*³³ involved all consecutive admissions, not just those requiring sedation.

†Conversion ratio of 2:1 can be used from oral morphine equivalent (OME) to parenteral morphine equivalent (PME). Consensus statement of the European Association for Palliative Care.³⁴

‡Combined results of a multicentre study.

Communication

All patients and/or their families were fully informed and consented to the use of sedation. In the case of the delirious patients, the closest family member gave consent on their behalf.

Ethical approval

Approval to conduct this research project was obtained from the ethics committees of Sungardens Hospice and the University of Cape Town.

Discussion

Terminology

Mild sedation, especially with benzodiazepines, is commonly used in palliative care to relieve insomnia and mild anxiety unresponsive to non-drug measures. Patients with severe symptoms such as agitated delirium, dyspnoea, intractable vomiting, convulsions and severe pain may require large doses of a variety of drugs, including anti-emetics, opioids, neuroleptics, anticonvulsants and even anaesthetic agents such as ketamine, all of which may cause some degree of sedation as a side-effect.⁹⁻¹¹

Deep sedation, enough to induce complete loss of consciousness, is occasionally needed in extreme situations in dying cancer patients when massive haemorrhage, massive

pulmonary embolism or complete airway obstruction occurs.¹¹⁻¹⁴

Only 1 patient included in this study required IV midazolam for sudden severe dyspnoea. Before this he had been extremely ill with advanced carcinoma of the pancreas complicated by partial intestinal obstruction, severe jaundice and a left-sided pleural effusion. He began vomiting, then developed severe dyspnoea and coughed up frothy pink sputum. He may have aspirated or developed acute pulmonary oedema. He did not respond to oxygen, IV furosemide or IV fentanyl, so midazolam was given very slowly intravenously. A total dose of 7.5 mg was eventually given before his distress subsided. The patient died 10 minutes later. This dose is higher than the usual loading dose of 0.5 - 1.5 mg recommended in normal circumstances.⁹ However, in such an emergency in a dying patient, an anaesthetising dose of a rapidly acting sedative, such as midazolam, is recommended.¹⁰

Terminal restlessness has many different causes.^{7,11} Drug toxicity, hypercalcaemia, urine retention and faecal impaction can be corrected relatively easily; however, in many patients terminal restlessness is multifactorial and irreversible. In such situations, sedation is an effective option.

Many doctors and nurses have reservations about the use of deep sedation in dying patients. Is sedation being used because of lack of skill in controlling terminal symptoms by non-sedating means? Is such sedation merely euthanasia in disguise?^{7,14,15} Is 'terminal sedation' a self-fulfilling prophecy, especially if the normal means of sustaining life such as food



and water have been withdrawn at the same time that sedation has been introduced?

Concern about these issues has prompted some to propose new terms to replace terminal sedation. After conducting a survey of 61 international experts in 1998, Chater *et al.*¹⁶ proposed that the phrase 'sedation for intractable distress in the dying' be used in place of terminal sedation. However, this is a rather cumbersome term.

Morita *et al.*¹⁷ have suggested that the term 'palliative sedation therapy' be used. They define this as 'the use of sedative medications to relieve untraceable and refractory distress by reduction in patient consciousness'. The term 'palliative sedation' removes the stigma associated with terminal sedation and places the emphasis on the purpose of the sedation rather than on the outcome. It sets out clearly the aim, the means and the extent of the sedation.

However, if sedation is seen as the desired outcome, it may discourage regular review and a continued search for non-sedating alternatives. Regular review is a hallmark of good care and should continue even when sedation is used. The amount of sedation can sometimes be reduced after the distress has been relieved for a short while.¹⁸⁻²⁰ In other cases the sedation needs to be continued until the patient dies.

Sedation and life expectancy

It is interesting to note that sedation of patients with advanced cancer does not necessarily mean the shortening of life. Several authors have documented no difference in survival of both sedated and non-sedated terminal patients.^{5,6,18,21} These are important findings and they go a long way towards establishing the legitimacy of the use of sedation in such patients.

In the series of studies reviewed by Sales,¹ delirium (39%) and dyspnoea (38%) were the main refractory symptoms for which sedation was used. Nausea and vomiting were refractory in 6%. The reason for the high incidence of intractable vomiting at Sungardens was that there were 5 patients (25%) with intestinal obstruction in a relatively small total number (20) of patients.

Lack of uniform diagnostic criteria and the reporting of more than 1 refractory symptom make comparison between the results from Sungardens and other surveys difficult. The median frequency of the use of sedation in the 13 studies reviewed by Sales¹ was 25%. The prevalence of sedation at Sungardens (20%) is below this figure.

The studies reviewed by Sales showed survivals of between 1.5 and 3.9 days after beginning sedation. The short survival of sedated patients has been shown to be a reflection of their advanced stage of disease rather than the shortening of their lives due to sedation.^{5,6,21}

The absence of a resident doctor at Sungardens Hospice

contributed to a rather long delay in achieving complete relief of the refractory symptoms, once sedation had begun. A second factor was that the drugs used for sedation were administered by continuous SC infusion using a syringe driver. Although this means that the onset of sedation is slower, it does not cause rapid over-sedation of patients and does not require an IV line. Continuous SC infusion by means of a syringe driver is commonly used in palliative care internationally.²²

Parenteral fluids are seldom used at Sungardens Hospice. Most terminally ill patients stop eating and drinking during the last few days of life without this causing them any discomfort. The body's metabolism undergoes a number of significant changes as a result of diminished intake of food and fluids. The metabolic rate slows down. Ketones and free fatty acids, produced by the catabolism of the body's own tissues, become the main energy source. The process of catabolism also produces water. Together with the reduction in the amount of urine excreted, this means that the need for additional fluids is greatly reduced.^{23,24} Although the actual needs of a sedated dying person for food and fluids are not known, there is no evidence that artificial feeding positively influences their comfort or outcome.²⁵ There is some evidence that artificial feeding may do just the opposite.²⁶⁻²⁸ The main problem, however, may be the symbolic nature of food and water. Denying them to anyone, even someone who is dying, may be perceived as cruel.²⁹ Open communication with patients and their families helps to ensure that joint decisions are made as far as possible. At the same time it should be emphasised that the main goal of care for the imminently dying person is comfort. Any plan of action must be aimed primarily at making the dying person comfortable. 'A doctor has neither the duty nor the right to prescribe a lingering death.'³⁰

The dose of drugs for analgesia and sedation used at Sungardens Hospice is similar to that used in other centres around the world. Turner and colleagues³¹ from Sydney reported a mean daily dose of 66.2 mg of parenteral morphine and a dose range of midazolam of 2.5 - 47 mg during the last 3 days of life. Thorns and Sykes³² from London report a mean daily dose of 55.5 mg of parenteral morphine in a series of terminal patients. Morita and colleagues³³ in Japan reported using a mean dose of 68 mg of morphine, 26 mg of midazolam and 5 mg of haloperidol per day (Table II). These three studies were reporting on the drug use of a sequence of consecutive admissions and not specifically on those being sedated for refractory symptoms. In a multicentre international study of the use of sedation for refractory symptoms, Fainsinger reported that the mean daily dose of midazolam was 33 mg (range 5 - 180 mg).⁸

Although comparing results is difficult as the designs of the studies are so different, the drug doses used at Sungardens Hospice appear to be similar to those used in other centres in England, Japan and Australia. They are also within the range suggested in standard textbooks of palliative medicine.^{9,34}



Limitations

The small numbers in this study preclude generalisation. The study highlights the need for clear definitions and guidelines to ensure the best possible care for those patients nearing the end of their lives who have intractable symptoms.

Conflict of interest

No external funding was received.

Conclusion

This survey shows that the use of sedation in dying patients at Sungardens Hospice is in line with several studies reported in the international literature. An international consensus is gradually emerging as common terminology and approaches are being adopted. A new multicentre international study using a standardised protocol is needed to confirm this consensus especially with regards to the indications for sedation and the drug dosages.

References

1. Sales JF. Sedation and terminal care. *Eur J Palliat Care* 2001; 8: 97-100.
2. Billings JA, Block SD. Slow euthanasia. *J Palliat Care* 1996; 12: 21-30.
3. Yanow ML. Responding to terminal suffering (letter). *Ann Intern Med* 2000; 135: 560.
4. Krakauer EL. Responding to terminal suffering (letter). *Ann Intern Med* 2000; 135: 560.
5. Ventafredda V, Ripamonti C, de Conno F, Tamburini M. Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care* 1990; 6: 7-11.
6. Morita T, Tsunoda J, Inoue S, Chihara S. Do hospice clinicians sedate patients to hasten death? *J Palliat Care* 1999; 15: 20-23.
7. Hardy J. Sedation in terminally ill patients. *Lancet* 2000; 356: 1866-1867.
8. Fainsinger RL, Waller A, Bercovici M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med* 2000; 14: 257-265.
9. Swarm RA, Cousins MJ. The management of intractable pain. In: Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine*. 2nd ed. Oxford: Oxford University Press, 1997: 406-408.
10. Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. *J Palliat Care* 1994; 10: 31-38.
11. Twycross R. *Symptom Management in Advanced Cancer*. 2nd ed. Oxon: Radcliff Medical Press, 1997: 111-115.
12. Twycross R, Lichter I. The terminal phase. In: Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine*. 2nd ed. Oxford: Oxford University Press, 1997: 977-992.
13. Jones DK, Davies RJ. Massive haemoptysis. *BMJ* 1990; 300: 889-890.
14. Macleod AD. The management of delirium in hospice practice. *Eur J Palliat Care* 1997; 4: 116-120.
15. Orentlicher D. The supreme court and physician assisted suicide. *N Engl J Med* 1997; 337: 1236-1239.
16. Chalser S, Viola R, Paterson J, Jarvis V. Sedation for intractable distress in the dying: a survey for experts. *Palliat Med* 1998; 12: 255-269.
17. Morita T, Tsuneto S, Shima Y. Proposed definitions for terminal sedation. *Lancet* 2001; 358: 335-336.
18. Fainsinger RL, de Moissac D, Mancini I, Oneschuk D. Sedation for delirium and other symptoms in terminally ill patients in Edmonton. *J Palliat Care* 2000; 16: 5-10.
19. Morita T, Inoue S, Chihara S. Sedation for symptom control in Japan: The importance of intermittent use and communication with family members. *J Pain Symptom Manage* 1996; 12: 32-38.
20. Fainsinger RL. Use of sedation by a hospital palliative care support team. *J Palliat Care* 1998; 14: 51-54.
21. Stone P, Phillips C, Spruyt O, Waight C. A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliat Med* 1997; 11: 493-494.
22. Roberts CJC, Keir S, Hanks GWC. The principles of drug use in palliative medicine. In: Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine*. 2nd ed. Oxford: Oxford University Press, 1998: 228-229.
23. Harris RA, Crabb DW. Starve-feed cycle. In: Devlin TM, ed. *Textbook of Biochemistry with Clinical Correlations*. 5th ed. New York: Wiley-Liss, 2002: 864-876.
24. Stanton BA, Koeppen BM. Control of body fluid osmolality and volume. In: Berne RM, Levy MN, Koeppen BM, Stanton BA, eds. *Physiology*. 5th ed. St. Louis: Mosby, 2003: 659 - 684.
25. McCann RM, Hall WJ, Groth-Juncker A. Comfort care for terminally ill patients: The appropriate use of nutrition and hydration. *JAMA* 1994; 272: 1263-1266.
26. Scott AG, Austin HE. Nasogastric feeding in the management of severe dysphagia in motor neurone disease. *Palliat Med* 1994; 8: 45 - 49.
27. Groher ME. Ethical dilemmas in providing nutrition. *Dysphagia* 1990; 5: 102-109.
28. Viola RA, Wells GA, Petersen J. The effects of fluid status and fluid therapy on the dying: a systemic review. *J Palliat Care* 1997; 13: 41-52.
29. McInerney F. Provision of food and fluids in terminal care: a sociological analysis. *Soc Sci Med* 1992; 34: 1271-1276.
30. Twycross R. *Symptom Management in Advanced Cancer*. 2nd ed. Oxon: Radcliffe Medical Press, 1997: 3.
31. Turner K, Chye R, Aggarwal G, Philip J, Skeels A, Lickiss JN. Dignity in dying: A preliminary study of patients in the last three days of life. *J Palliat Care* 1996; 12: 7-13.
32. Thorns A, Sykes N. Opioid use in the last week of life and implications for end of life decision-making. *Lancet* 2000; 356: 398-399.
33. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manage* 2001; 21: 282-289.
34. Twycross R. *Pain Relief in Advanced Cancer*. Edinburgh: Churchill-Livingstone, 1994: 255-276.

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