Internal Medicine Journal 2005; 35: 512–517

ORIGINAL ARTICLE

Effects of opioids and sedatives on survival in an Australian inpatient palliative care population

P. D. GOOD, P. J. RAVENSCROFT and J. CAVENAGH

Division of Palliative Care, Newcastle Mater Misericordiae Hospital, Waratah and Faculty of Health, University of Newcastle, Callaghan, New South Wales, Australia

Abstract

Aims: To assess whether opioid and sedative medication use affects survival (from hospice admission to death) of patients in an Australian inpatient palliative care unit.

Background: Retrospective audit. Newcastle Mercy Hospice – a tertiary referral palliative care unit. All patients who died in the hospice between 1 February and 31 December 2000.

Methods: Length of survival from hospice admission to death, and the median and mean doses of opioids and sedatives used in the last 24 h of life. Comparison of these with published studies outside of Australia.

Results: In this study, the use of opioids, benzodiazepines and haloperidol did not have an association with shortened survival and the only statistical significant finding was an increased survival in patients who were on 300 mg/day or more of oral morphine equivalent (OME). The proportion of patients requiring greater than or equal to 300 mg OME/day (at 28%) was higher than published studies, but the mean dose of 371 mg OME/day was within the range of other studies. The proportion of patients receiving sedatives (94%) was higher than other studies, but the median dose of parenteral midazolam equivalent of 12.5 mg per 24 h was lower than other studies from outside Australia.

Conclusions: There was no association between the doses of opioids and sedatives on the last day of life and survival (from hospice admission to death) in this population of palliative care patients. (Intern Med J 2005; 35: 512–517)

Key words: palliative care, survival analysis, narcotics/ therapeutic use, hypnotics and sedatives/ therapeutic use, double effect.

INTRODUCTION

There is a perception in medicine and the wider community that symptom control in palliative care is associated with the hastening of death. This seems mainly based on the idea that morphine in particular, and more recently sedative medications, relieves symptoms but leads to a premature death. Some commentators have dubbed this 'slow euthanasia',[1] whilst others have been critical of this term and thinking.[2–4] The idea that symptom control may be associated with hastening death is a common feature of codes of ethics of different medical organizations. For example, the Australian Medical Association states that terminally ill patients have the right 'to receive treatment for pain and suffering, even when such therapy may shorten a patient's life'.[5] This thinking is based on the ethical concept of the principle of double-effect. This so called double-effect reasoning has been initially attributed to Thomas Aquinas (in relation to self-defence) and more recently developed by others.[6] The conditions of this principle that must be met in relation to medical treatment are:[7–9]

- The treatment must have potential beneficial and harmful effects
- The clinician intends the beneficial effect (relief of symptoms), but the foreseen harmful effect (hastening death) may be unavoidable
- The harmful effect (death) is not necessary to achieve the beneficial effect (relief of symptoms)
- The beneficial effect must outweigh the harmful effect (i.e. the relief of suffering is a compelling reason to justify the risk of the harmful effect)

Questioning of the use of this ethical principle has occurred, based on a clinician's intentions.[10] However, more recent studies have looked at the question of whether the idea of hastened death with opioid/sedative use is clinically correct.

There have been previous studies from Japan,[11] England[12] and Israel[13] that have looked at opioid use and survival from time of admission to a hospital or palliative care unit to death. None has shown that opioid usage influences survival. All have had a different methodology, with some looking at different levels of morphine use and survival. Others like Thorns and Sykes have looked at the change in morphine dosage and survival, based on the idea that the rate of change in

Correspondence to: Phillip Good, Newcastle Mater Misericordiae Hospital, Division of Palliative Care, Locked Bag 7, Hunter Region Mail Centre, Warabrook, NSW 2310, Australia.
Email: Phillip.Good@mater.health.nsw.gov.au

Received 16 August 2004; accepted 25 January 2005.

Funding: None

Potential conflicts of interest: None

dosage may be a more important factor than total dose. They found that survival was not related to the rate of increase in dose, and that a large increase in the dose of opioids was not more likely to occur in the last 48 h of a patient's life.[12]

Studies have been performed in Japan,[11] England,[9,14] Germany,[15] Italy[16] and Taiwan[17] looking at sedative use and survival in terms of time from admission (to an outpatient palliative care programme or an inpatient facility) till death. Again all have had a different methodology and none has shown an influence of sedative use on survival.

The use of sedatives as opposed to the practice of sedation has been much talked about in the literature. Midazolam and haloperidol are the most commonly used sedative medications in palliative care.[9] Benzodiazepines are used to treat anxiety, nausea and vomiting, delirium, seizures, myoclonus and dyspnoea, whereas haloperidol is most commonly used to treat delirium (including terminal agitation), nausea and vomiting.[18–20] The other use of sedative medications is as part of a regime to treat symptoms that are refractory to standard palliative treatments. Morita *et al.* have defined this as 'the use of sedative medications to relieve intolerable and refractory distress by the reduction in patient consciousness'.[21] It is difficult in reviewing studies, looking at sedative use, to define clearly and objectively whether the use was as part of standard symptom control or as part of treatment of refractory symptoms. This may be a result of retrospective studies or that there is a continuum between the two. The other controversy about sedative use has been the variation of doses used according to different countries. This was highlighted in a multicentre international study looking at 'sedation for uncontrolled symptoms in terminally ill patients'.[22] The median dose of midazolam used varied between 15 mg/day (Israel and South Africa) to 52 mg/day in Spain. The reasons for the variation are unclear but the authors suggested differences in culture, truth-telling and previous benzodiazepine exposure.

It is unclear where the practice of Australian palliative care falls in the use of opioids and sedatives, and whether their use has any effect on survival of terminally ill patients. A small study has looked at 50 patients in regards to dignity in dying, and found that 88% of patients used benzodiazepines in the last 3 days of life (total dosage of midazolam varied from 2.5 to 47 mg in those last 3 days), 86% of patients used opioids with a mean daily dose of 198.6 mg of oral morphine equivalent (OME)/day.[23] However, that study did not look at survival with regards to opioid and sedative use. Therefore, this present study was carried out with the aims of recording the median dosage of opioids and sedatives used in the last 24 h of life; examining whether there is any effect on survival in the hospice according to different doses of opioids or sedatives; and to compare these results to previously published international studies, performed with a similar methodology.[11,13]

This present study was a retrospective review of use of opioids and sedatives in the last 24 h of life. The retrospective nature of this review ensured that no bias was able to occur due to doctors knowing about the study and possibly changing their practice. The patients were in the Newcastle Mercy Hospice, a 20-bed freestanding building on the same grounds as the Newcastle Mater Misericordiae hospital. The hospital is the main cancer referral centre for the Hunter region of New South Wales. The Hunter region has a population of approximately 540 000 people. The Newcastle Mercy Hospice is the inpatient unit of the Newcastle palliative care service. This is an integrated service consisting of inpatient beds, community care and consultation service. A previous study has described the characteristics of patients on the service and found the median survival was 54 days (from the time of referral till death).[24] Patients can be referred to the inpatient hospice for admission if they are on any of the Hunter Area palliative care services, have the consent of their general practitioner or specialist, and fit the hospice criteria of admission for symptom control, terminal care or respite. The medical practitioners who work in the hospice include three palliative care specialists who rotate through the hospice, supported by junior medical staff consisting of one registrar level and one senior resident medical officer level during the time of this study. Further after hours assistance is provided by general practitioners who have a special interest in palliative care.

METHODS

The medical record and medication charts of hospice patients were reviewed for all deaths between 1 February and 31 December 2000. During this period there were 545 admission to the hospice, with 232 deaths; medical records could only be obtained for 229 patients. No record was made of the intent of the use of sedative medication, as the intention was not clear from review of the records – this study simply looked at the doses recorded and the survival of the patient.

Opioid dosages were converted to their OME for comparisons.[25] Benzodiazepines were converted to parenteral midazolam equivalent (PME) using parenteral midazolam 5 mg = diazepam 5 mg, and following a published table.[26]

The patients were then split into groups according to the respective PME and OME. Groupings chosen were based on previous studies in this area. The first grouping for PME was (≤10 mg, >10 mg) as determined by Sykes and Thorns,[27] and the second as defined by Morita *et al.* was 0 (not used), 1 (0.5–29.5 mg PME/24 h) and 2 (≥30 mg PME/24 h).[11] OME was stratified to: 0 (<120 mg OME/24 h), 1 (120–299.5 mg OME/24 h) and 2 (≥300 mg OME/24 h).[11,13]

Using these groupings, the patients were compared for length of stay in the hospice (admission to death). The use of haloperidol was reviewed as well. Survival curves were calculated by the Kaplan–Meier method, with the log rank test used to compare groups. The *P*-values found in the calculations are on the survival curves (Figs 1,2). Statistical analysis was performed using StatsDirect software (Version 2.3.8; StatsDirect Ltd, Sale, UK).

RESULTS

Demographics

The median age of death was 72 years. The median length of stay (admission till death) in the hospice was 8 days. The median time from referral, to the palliative care programmes, until death was 57 days in the Newcastle service. The male : female ratio was 59:41 for the hospice.

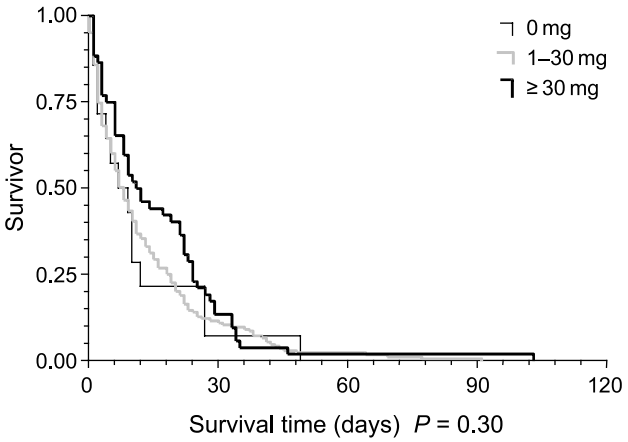

Figure 1 Survival plot: parenteral midazolam equivalent per 24 h.

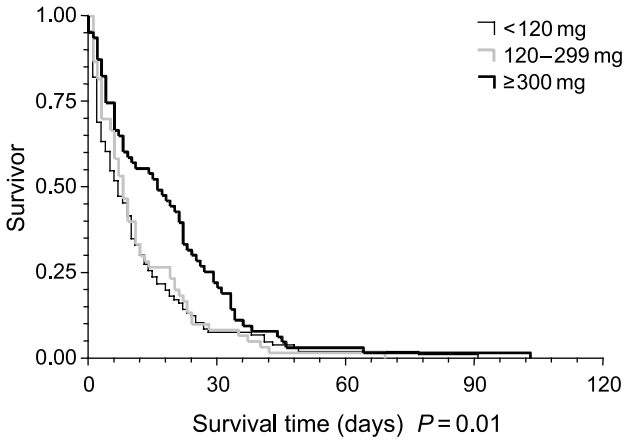

Figure 2 Survival plot: oral morphine equivalent per 24 h.

The most common diagnoses of patients who died in the hospice were: lung (20%), colorectal (12%), gastroesophageal (10%), prostate (9%) and breast (8%) cancer.

Medications

Opioids were used most frequently, closely followed by benzodiazepines, with haloperidol used at a much lower frequency (Table 1).

Opioid doses were divided into three different groups according to the previous study carried out by Morita *et al.*[11] (Table 2). Opioids administered were: codeine (n = 1 patient), fentanyl (50), sufentanil (3), hydromorphone (1), morphine subcutaneous (184), oral morphine (29), oxycodone (1) and pethidine (1).

Benzodiazepine doses were divided in two different ways (Table 2). There was no significant difference between these groups in relation to survival (P = 0.45, log–rank test (Sykes categories) and P = 0.30, log–rank test (Morita categories)).

Haloperidol usage is shown in Table 1. This was divided simply according to non-used or any dose used. There was no significant difference in survival between these two groups (P = 0.90, log–rank test).

The survival curves according to the different categories are shown in Figures 1 and 2.

The only significant finding was with the OME and the finding that those patients on ≥300 mg/day had a longer survival time (from hospice admission to death), compared to patients on 120–299 mg/day and those on less than 120 mg/day (P = 0.01, log–rank test).

Tables 3 and 4 show a comparison of results of this study to previously published international studies.

DISCUSSION

This present study looked at the survival (from the time of hospice admission to death) in patients on opioids and sedatives in the last 24 h of life.

The use of opioids, benzodiazepines and haloperidol did not have an association with shortened survival and this is similar to other previous studies.[11–17,27,28] The only statistical significant finding was an increased survival in patients who were on ≥300 mg/day OME. The reasons why this group had a longer survival are unclear from this study. The most likely reason is that this group of patients represents a group of complex pain syndromes and as a result was admitted to the hospice earlier, needing higher doses of opioids to control their symptoms. The other possibilities are that this group of

Table 1 Opioids and sedatives in the last 24 h

	Frequency *n* (%)	Mean dose (mg/24 h) (95%CI)	Median dose (mg/24 h)	Range (mg/24 h)
Opioids (OME)	222 (97)	370.7 (287.4–454)	135	2–4710
Benzodiazepines (PME)	215 (94)	21.9 (18.2–25.6)	12.5	1–250
Haloperidol	82 (36)	3.2 (2.9–4.3)	2.5	0.2–15

OME, oral morphine equivalent; PME, parenteral midazolam equivalent.

Table 2 Oral morphine equivalent and parenteral midazolam equivalent

	n (%)	Median survival (days)	Mean survival (95%CI) (days)	Range (days)
OME/24 h				
<120 mg	106 (46)	7	11.4 (8.6–14.2)	0–91
120–299 mg	60 (26)	8	12.7 (9.3–16)	1–69
>300 mg	63 (28)	16	18.3 (14–22.6)	0–103
PME/24 h				
0 mg	14 (6)	7	11.9 (4.7–19.0)	1–49
>0 and <30 mg	163 (71)	8	12.9 (10.6–15.3)	0–91
≥30 mg	52 (23)	11	16.6 (12.0–21.2)	1–103
PME/24 h				
≤10 mg	108 (47)	8	13.0 (10.0–16.1)	0–91
>10 mg	121 (53)	9	14.3 (11.6–16.9)	0–103

OME, oral morphine equivalent; PME, parenteral midazolam equivalent.

Table 3 Comparative frequency of medication use

	Frequency (%)	Frequency (Morita *et al.*)[11] (%)	Frequency (Sykes & Thorns)[27] (%)	Frequency (Thorns & Sykes)[12] (%)
Opioids (OME)	97	82	–	89
Benzodiazepines (PME)	94	27	82	–
Haloperidol	36	43	35	–

OME, oral morphine equivalent; PME, parenteral midazolam equivalent; –, not applicable.

Table 4 Comparative median doses

	Median dose (mg/24 h)	Median dose (mg/24 h) (Morita *et al*)[11]	Median dose (mg/24 h) (Thorns & Sykes)[12]	Median dose (mg/24) (Sykes & Thorns)[27]
Opioids (OME)	135	40	79.2	–
Benzodiazepines (PME)	12.5	10	–	23.0–52.5
Haloperidol	2.5	3.8	–	–

OME, oral morphine equivalent; PME, parenteral midazolam equivalent; –, not applicable.

patients lived longer – directly as the result of higher opioid dosage, or from better pain control as a result of opioid use.

The proportion of patients requiring greater than or equal to 300 mg OME/day was higher in this present study (28%) than two previously published studies (12.1%,[13] 7.7%[11]). However, the mean dose of 370.7 mg OME/day is within the range of other studies of morphine use before death, i.e. 167 mg to 1977 mg OME/day.[12,23,28–32] Whilst the median doses are shown in Table 4, mean doses are more commonly reported in published studies. Again these patients probably represent a group of complex pain syndromes for which patients are commonly admitted to our inpatient unit. The hospice is the only tertiary referral palliative care unit for a large population and large area in New South Wales, and as such is the likely place where the most complex symptomatology is seen amongst mainly oncological patients. This service also has a comprehensive community component and this means that patients are not generally admitted to the hospice unless their symptoms are difficult or complex.

The proportion of patients receiving sedatives (94%) is higher than the 1–88% found in a recent review of sedative use at the end of life.[9] Interestingly, the study where 88% of patients used benzodiazepines was also carried out in Australia.[23] The median dose of PME of 12.5 mg per 24 h is lower than most previously published studies (15–53 mg/24 h PME[11,22,27,33]). The increased frequency, but lower median dosages, suggests

that sedative use in this setting most likely represents 'normal' symptom control as opposed to 'sedation for uncontrolled symptoms in terminally ill patients.[22] It is rare in this unit that patients are deliberately sedated with the aim of unconsciousness. However, treatment of anxiety is a priority of the unit. Anxiety is a very common symptom in palliative care and there has been little written about it in this setting. One recent study found that 48% of patients had anxiety (defined as a score >7 on the Hospital Anxiety and Depression Scale – Anxiety Subscale) in a cross-sectional observation study of 178 cancer patients.[34] As well as treatment of anxiety, benzodiazepines are frequently used in the treatment of delirium at the end of life.

Whilst the proportion of patients receiving haloperidol was similar to a study in Japan[11] (36% vs 43%), the median dosage was slightly lower in this study (2.5 mg vs 3.8 mg per 24 h). Haloperidol is used as first line therapy for delirium. As delirium is one of the commonest indications for sedation in palliative care settings,[9] it may be the reason lower benzodiazepine doses are used is because of the increased frequency of haloperidol use.

There are several limitations of this study. First, it is retrospective and data may be incomplete. Whilst the retrospective nature of the study may be a limitation, it could also be considered an advantage so that no bias in medication use was apparent. Generalization is difficult, as this was an Australian population in an inpatient palliative care setting. As well, all opioid and sedative use was titrated to patients' symptoms and their use in other medical settings may be different. The methodology of all studies in this difficult area is open for criticism. The groups that are compared are not truly matched groups (i.e. they are not randomized nor even controlled groups). Whilst this is a limitation, it is difficult to see that in this population it will ever be possible to perform a truly matched comparison to evaluate causality. Rather, we are left with studies that look for an association between opioid/sedative use and length of survival.

The principle of double effect seems to have 'stuck' to the use of opioid medication in particular, and more recently, sedative medication. There is a stigma attached to these medications that they are dangerous and likely to shorten survival, but that their use is justified because of double-effect reasoning. This study adds to the weight of growing evidence from similar studies around the world that opioid and sedative medications are safe drugs and their use does not influence survival of palliative care patients. Clinicians should be confident in their safety and efficacy as long as their administration is in a similar manner to this study, that is, titrated to patients' symptoms.

The reality of palliative care (and hopefully medicine in general) is that it is rarely necessary to use the principle of double-effect as a justification for the administration of opioids and sedatives.

ACKNOWLEDGEMENTS

The authors would like to thank all the palliative care staff who record important data, and especially Jan Burns who maintains the database.

REFERENCES

1 Billings JA, Block SD. Slow euthanasia. J Palliat Care 1996; 12: 21–30.
2 Mount B. Morphine drips, terminal sedation, and slow euthanasia: definitions and facts, not anecdotes. J Palliat Care 1996; 12: 31–7.
3 Wall PD. The generation of yet another myth on the use of narcotics. Pain 1997; 73: 121–2.
4 Fohr S. The double effect of pain medication: separating myth from reality. J Palliat Med 1998; 1: 315–28.
5 Australian Medical Association. AMA Code of Ethics 2003. [cited 2003 October 30]. Available from: URL: http://www.ama.com.au/web.nsf/doc/WEEN-5M4VJV
6 Kaczor C. Double-effect reasoning from Jean Pierre Guy to Peter Knauer. Theol Studies 1998; 59: 297–316.
7 Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. J Palliat Care 1994; 10: 31–8.
8 Beauchamp TL, Childress JF, eds. Principles of Biomedical Ethics, 5th edn. New York: Oxford University Press; 2001: 207.
9 Sykes N, Thorns A. The use of opioids and sedatives at the end of life. Lancet Oncol 2003; 4: 312–18.
10 Quill TE. The ambiguity of clinical intentions. N Engl J Med 1993; 329: 1039–40.
11 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: 282–9.
12 Thorns A, Sykes N. Opioid use in last week of life and implications for end-of-life decision-making. Lancet 2000; 356: 398–9.
13 Bercovitch M, Waller A, Adunsky A. High dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy. Cancer 1999; 86: 871–7.
14 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: 140–4.
15 Muller-Busch HC, Andres I, Jehser T. Sedation in palliative care – a critical analysis of 7 years experience. BMC Palliat Care 2003; 2: 2.
16 Ventafridda V, Ripamonti C, De Conno F, Tamburini M, Cassileth BR. Symptom prevalence and control during cancer patients' last days of life. J Palliat Care 1990; 6: 7–11.
17 Chiu TY, Hu WY, Lue BH, Cheng SY, Chen CY. Sedation for refractory symptoms of terminal cancer patients in Taiwan. J Pain Symptom Manage 2001; 21: 467–72.
18 McNamara P, Minton M, Twycross R. Use of midazolam in palliative care. Palliat Med 1991; 5: 244–9.
19 Bottomley DM, Hanks GW. Subcutaneous midazolam infusion in palliative care. J Pain Symptom Manage 1990; 5: 259–61.
20 Stiefel F, Fainsinger R, Bruera E. Acute confusional states in patients with advanced cancer. J Pain Symptom Manage 1992; 7: 94–8.
21 Morita T, Tsuneto S, Shima Y. Definition of sedation for symptom relief: a systematic literature review and a proposal of operational criteria. J Pain Symptom Manage 2002; 24: 447–53.
22 Fainsinger RL, Waller A, Bercovici M, Bengtson K, Landman W, Hosking M *et al.* A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. Palliat Med 2000; 14: 257–65.
23 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.
24 Good PD, Cavenagh J, Ravenscroft PJ. Survival after enrollment in an Australian palliative care program. J Pain Symptom Manage 2004; 27: 310–15.

25 Doyle D, Hanks GWC, MacDonald N. Oxford Textbook of Palliative Medicine, 2nd edn. New York: Oxford University Press, 1998.
26 Twycross RG. Symptom Management in Advanced Cancer. Oxford: Radcliffe Medical Press; 1995.
27 Sykes N, Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. Arch Intern Med 2003; 163: 341–4.
28 Morita T, Ichiki T, Tsunoda J, Inoue S, Chihara S. A prospective study on the dying process in terminally ill cancer patients. Am J Hosp Palliat Care 1998; 15: 217–22.
29 Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 1992; 10: 149–55.
30 Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T. Symptom control during the last week of life on a palliative care unit. J Palliat Care 1991; 7: 5–11.
31 Fainsinger RL, Louie K, Belzile M, Bruera E, Hanson J. Decreased opioid doses used on a palliative care unit. J Palliat Care 1996; 12: 6–9.
32 Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain 1995; 63: 65–76.
33 Fainsinger RL, Landman W, Hoskings M, Bruera E. Sedation for uncontrolled symptoms in a South African hospice. J Pain Symptom Manage 1998; 16: 145–52.
34 Stark D, Kiely M, Smith A, Velikova G, House A, Selby P. Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. J Clin Oncol 2002; 20: 3137–48.